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THROMBOCYTOPENIA AND HYPOCALCEMIA

A NEW METHOD FOR THEIR PRODUCTION IN DOGS AND AN EVALUATION OF THEIR SIGNIFICANCE IN ABNORMAL BLEEDING

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SINCE the publication by Duke[9] demonstrating the existence of a thrombocytopenia in certain patients with abnormal bleeding, much has been written about the frequent association of low circulating platelet levels with clinical evidences of abnormal bleeding. The subsequent accumulation of evidence for this association has contributed to the acceptance by many clinicians of the etiologic role of thrombocytopenia in the production of abnormal bleeding with a host of clinical conditions. Spaet[22, 23] and Craddock[6, 7] have pointed out that simple thrombocytopenia has not been demonstrated to be the cause of a hemorrhagic diathesis and that the role of platelets in the production of abnormal bleeding is as yet unknown.

Recent publications[8, 12-14, 17, 21, 24] have demonstrated low platelet levels in patients with the syndrome of "hemorrhage following massive transfusion." A few of these authors infer that thrombocytopenia plays a major etiologic role in the production of abnormal bleeding seen with this syndrome. It has also been suggested that citrate intoxication caused abnormal bleeding by depressing the ionized calcium content of the blood.[4, 5, 25]

This study was undertaken to help clarify the role of low circulating platelet and calcium levels in the production of abnormal bleeding.

The interesting property of certain cation exchange resins to adsorb calcium and platelets has been known to investigators for years.[1, 3, 10, 15, 16, 18, 19] We have used these phenomena in designing the following experiments.

DESCRIPTION OF TECHNIQUES

Thirteen mongrel dogs weighing 8 to 14 Kg. were used for this study. The dogs were anesthetized with intraperitoneal sodium pentobarbital (25 mg. per

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kilogram). The inguinal area was cleaned and shaved, and a cut-down on the femoral artery and vein was performed under clean but nonsterile conditions. The femoral artery was cannulated with stiff polyethylene tubing and the femoral vein was cannulated with the soft tubing obtained from a blood administration kit. In any given experiment one of two different techniques was used. In 5 experiments the blood passed through the arterial cannula into an airtight 250 c.c. siliconized bottle* filled with resin† (Fig. 1). In 8 experiments the arterial blood was allowed to flow into a large siliconized funnel containing 250 to 300 Gm. of resin (in place of the bottle shown in Fig. 1). In both techniques the blood then filtered slowly through the resin, was filtered, and then passed into the cartridge of a blood administration kit and from there into the tubing leading to the femoral vein. In both techniques the tubing and resin were filled with isotonic sodium chloride before the resin shunt was started. The average rate of blood flow through the resin column was 20 c.c. per minute. All blood samples were taken from the arterial cannula inserted in the femoral artery.

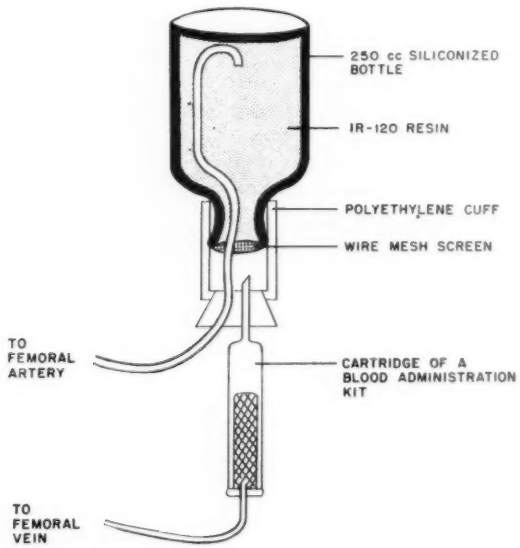


Fig. 1.

1. Platelet counts were performed within 60 minutes of sampling by the following technique. Nine parts of arterial blood from the femoral artery was allowed to flow into a siliconized glass test tube containing one part 3.8 per cent sodium citrate solution. After thorough mixing, the citrated blood was drawn up to the 0.05 mark of a R.B.C. pipette and the pipette was then filled with 1 per cent Sequestrine, Na_2 solution made isotonic with sodium chloride (0.7 Gm. NaCl per 100 c.c. solution). After the solution had been shaken, the suspension was placed in a standard Neubauer counting chamber and platelet counts were determined.

*Abbott Laboratories, North Chicago, Ill.

†Amberlite IR-120 obtained from Rohm & Haas, Resinous Products Division, Philadelphia, Pa.

2. Serum calcium levels were performed according to the technique of Rehell.[20]

3. We have employed Bell and Alton's lipid preparation from brain as a substitute for platelets in the thromboplastin generation test.[2]

4. Unless otherwise indicated all methods are those to be found in the book, *Blood Coagulation—Methods of Study,* edited by L. Tocantins, published by Grune & Stratton, Inc., New York, 1953.

RESULTS

In Table I are detailed the changes occurring in dogs' blood following passage through the resin system. Under each factor heading there are two columns: column 1 represents the values for the given factor in the dog's blood immediately before passage through the resin system; column 2 represents the values for the given factor of the same blood immediately after passage through the resin system. The average platelet count before passage through the resin was 203,000 per cubic millimeter and the same blood immediately after resination contained an average of 39,000 platelets per cubic millimeter. This represents an average drop of 81 per cent in platelet levels following passage through the resin. Similarly, there was an average of 7.3 mg. per cent calcium in the blood before and 1.9 mg. per cent calcium in the blood after passage through the resin column, representing an average drop of 74 per cent. There were no constant and significant changes occurring following passage through the resin for the thromboplastin generation test, the prothrombin consumption test, the one-stage prothrombin test, and the fibrinogen levels.

Table II demonstrates the changes which occurred in the dogs' corporeal circulating blood following the procedure previously outlined. Under each factor heading there are two columns: column 1 represents the values of the given factor in the animal's corporeal blood before starting the procedure; column 2 represents the values of the given factor in the animal's corporeal blood at the end of the procedure. The average circulating platelet levels before and after passage through the resin were 249,000 per cubic millimeter and 98,000 per cubic millimeter, respectively, representing an average fall of 61 per cent. It is noteworthy that 5 animals had circulating platelet levels of less than 50,000 per cubic millimeter following this procedure. The average circulating calcium levels before and after the procedure were 8.8 and 6.7 mg. per cent, respectively, an average drop of 26 per cent. The lowest calcium level obtained was 4.3 mg. per cent in experiment 27. It was noted in all experiments that after approximately 30 minutes of operation of the resin column the animal's blood pressure dropped to significantly low levels. In several cases calcium chloride was given intravenously followed by an immediate and dramatic rise in the blood pressure.

In most of these experiments the dogs' circulating prothrombin and fibrinogen levels were reduced following the procedure. In certain cases there was a marked reduction in the thromboplastin generation while in others no change was noted. The changes seen in the recalcified plasma clotting times were quite variable. The nature of these changes are further analyzed in

TABLE I. EFFECTS OF IN VITRO RESINATION OF DOGS' BLOOD

EXPERIMENT NUMBER	PLATELETS		THROMBOPLASTIN GENERATION TEST (%)		PROTHROMBIN CONSUMPTION (%)		CALCIUM (MG. %)		PROTHROMBIN (%)		FIBRINOGEN (MG. %)		RECALCIFIED PLASMA CLOTTING TIME (SECS.)	
	1	2	1	2	1	2	1	2	1	2	1	2	1	2
4	33	9	100	100					80	80	235	200	70	68
15	157	160	100	100	96	96	6.9	1.8	50	55	243	183	170	175
16	500	16					8.6	1.1			450	466	162	434
	390	46												
17	187	7					7.7	3.9	50	40	233	255	250	223
	143	10					7.0	0.9	45	40	251	230	173	165
	107	30					7.7	2.5	50	45	255	256	158	155
18	287	7	5	45			6.9	0.2	55	45	240	195	180	230
	120	57					6.0	1.3	30	48	198	180	180	115
	110	50	45	5					30	25	160	215	115	85

TABLE II. CHANGES IN COAGULATION STUDIES BEFORE AND AFTER RESINATION PROCEDURE

EXPERIMENT NUMBER	TIME ON RESIN SHUNT (MIN.)	PLATELETS (× 103)		THROMBOPLASTIN GENERATION TEST (%)		CALCIUM (MG. %)		PROTHROMBIN (%)		FIBRINOGEN (MG. %)		RECALCIFIED PLASMA CLOTTING TIME (SECS.)	
		1	2	1	2	1	2	1	2	1	2	1	2
4	90	33	36	100	100			80	85	235	200	70	56
9	60	170	60	100	45	8.6	5.7	80	18	224	100	105	244
10	60	100	40	100	12	12.5	6.6	60	*40	170	144	119	275
11	60	260	50	100	40	8.9	8.3	90	68	284	260	172	183
14	60	64	40	100	100	8.14	7.43	60	50	311	302	470	193
15	60	770	157	90	100	10.8	6.9	50	50	466	243	190	170
16	30	496	390			8.6				450		162	
17	120	293	107	100	45	10.0	7.7	55	50	328	255	165	158
18	120	317	110	90	45	8.6	7.1	60	30	189	160	238	115
27	70	130		100	100	7.8	4.3	80	60	530	308	183	168
28	70			100	50	4.7	5.2	60	65	155	148	215	233
29	80	237	67	100	90			80	60	215	190	102	145
34	30	120	23	100	85	8.2	7.7	65	50	281	232	235	252

1 = Sample from arterial canula before starting the procedure.

2 = Sample from arterial canula at end of the procedure.

*Calcium concentration used in performing test was adjusted so that final calcium concentration in mixture would approximate that in initial sample.

Figs. 2 through 7. These figures demonstrate the changes occurring in the coagulation components in the dogs' circulating blood while the apparatus described was in operation. They are therefore rough estimations of rates of change of the variables concerned during the time the dogs' blood was passing through the resin column. In Figs. 2 through 7, each point represents the average value of the experiments performed and is expressed in terms of percentage of initial premanipulative value. The abscissa expresses the length of time the animals' blood had been allowed to flow through the resin at the time the samples were taken. The vertical lines represent one sigma variation from the mean. In Fig. 7 the individual curves obtained from 7 experiments are plotted.

Figs. 2 and 3 show a rapid initial fall in platelets and calcium during the first 15 minutes on the resin column following which the rate of depletion of these variables is decreased. These roughly follow the logarithmic-type depletion curve expected from the theoretical considerations of Wiener and Wexler.[26] Figs. 4 and 5 reveal a linear depletion rate of fibrinogen and prothrombin. The changes in the recalcified clotting times seen in Fig. 6 are quite variable as noted by the wide sigma variations from the mean values. The individual curves of the thromboplastin generation test shown in Fig. 7 group themselves into two patterns. Experiments 14, 15, 27, and 29 show no change in thromboplastin generation, while experiments 7, 9, and 10 show dramatic changes with rates of depletion following a logarithmic pattern.

It must be emphasized that in none of the animals studied was there noted any evidences of petechiae, purpura, excessive oozing at incision sites, or other evidences of a hemorrhagic diathesis.

DISCUSSION OF RESULTS

The results of Table I indicate that Amberlite IR-120 resin on the sodium cycle used in the apparatus described is capable of removing significant amounts of platelets and calcium from dogs' whole blood. Other changes in the dogs' blood coagulation system are noted following this procedure. Since the dynamics of this procedure are similar to those of an exchange transfusion, the mathematic considerations of Wiener and Wexler are applicable in this situation. Accordingly, if a given factor were being removed from the blood in its passage through the resin, its rate of depletion curve should have a logarithmic form. The rate of depletion curves for platelets and calcium have such a logarithmic form, but the curves for prothrombin and fibrinogen do not. This is interpreted by us to be evidence against the concept that the prothrombin and fibrinogen were being removed from the blood by the resin. Although clotting along the walls of the apparatus used in this experiment might account for some of the depletion in circulating prothrombin and fibrinogen, a definite reason for their decrease is not apparent to us at the present time. The interesting groupings of thromboplastin generation test responses is being investigated at present in our laboratory.

Although platelet levels as low as 23,000 per cubic millimeter and calcium levels as low as 4.3 mg. per cent were produced, no evidences of abnormal

bleeding were noted. This is in agreement with the recent work of Craddock[7] who produced thrombocytopenia by leukophoresis. All of his animals had a final platelet count of 30,000 per cubic millimeter or less, but none of them de-

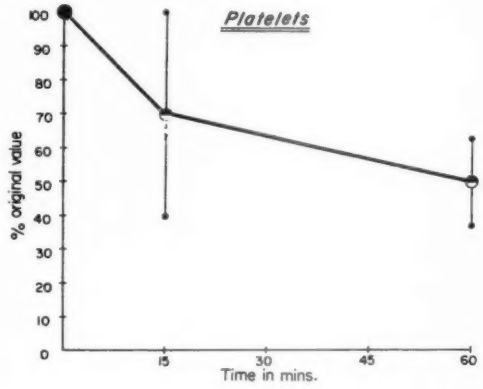


Fig. 2.

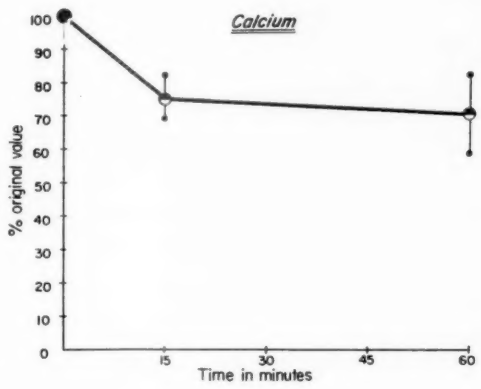
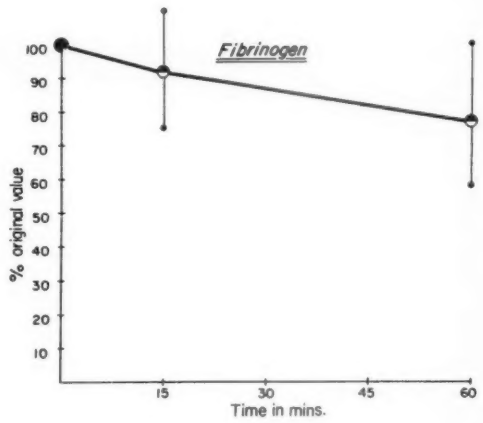


Fig. 3.



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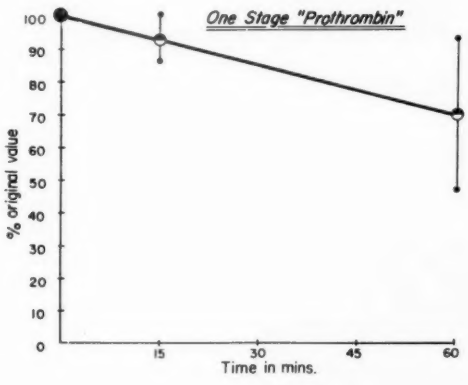

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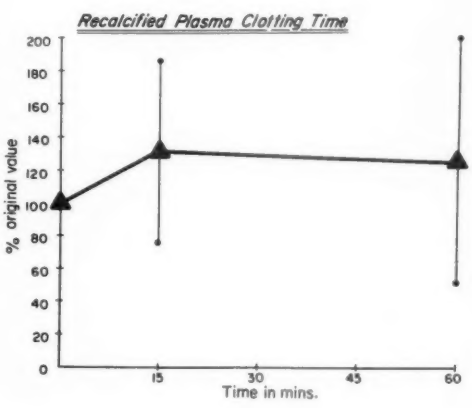

Fig. 6.

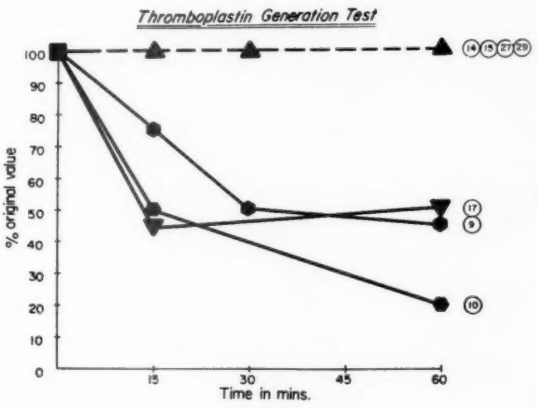

Fig. 7.

veloped any evidence of a hemorrhagic diathesis. He concluded that thrombocytopenia per se is not necessarily accompanied by abnormal bleeding unless some other abnormality is present. Spaet, in his thorough review of the literature[22] and in his own work,[23] has pointed out the frequent lack of correlation

between low platelet counts and clinical manifestations of abnormal bleeding. It is of interest that in the recent studies of the bleeding tendency seen following massive transfusions many investigators have noted the presence of a thrombocytopenia in the absence of constant defects in the other coagulation factors studied. However, studies being done in this laboratory,[11] on human beings who have received massive blood transfusions and have developed thrombocytopenia but have not shown evidence of abnormal bleeding, agree with the findings presented in this paper indicating no simple relationship between thrombocytopenia and bleeding.

In these experiments the hypocalcemia obtained apparently produced hypotensive effects without causing abnormal bleeding. If citrate intoxication produces its effects by depressing ionized blood calcium levels, it is doubtful that this condition would result in abnormal bleeding before the production of cardiovascular effects.

CONCLUSIONS

1. A new technique for the production of thrombocytopenia and hypocalcemia in dogs has been discussed.

2. The results of these studies indicate that the incrimination of thrombocytopenia or hypocalcemia as the sole cause of a hemorrhagic diathesis is not warranted.

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THROMBOCYTOPENIA IN MASSIVE TRANSFUSION

Mechanism of Production and Evaluation of Role in Producing Abnormal Bleeding

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DURING the Korean War, the occurrence of a hemorrhagic syndrome following massive blood transfusions in battle casualties was noted. Initial studies by Scott and Crosby[11] revealed a thrombocytopenia in these patients, but it was their feeling that the outstanding defect was a deficiency in blood clotting factor V. Subsequent studies confirmed the finding of thrombocytopenia but did not demonstrate a significant deficiency in factor V in this syndrome.[3, 8-10, 13] Krevans and Jackson[8] suggested that the thrombocytopenia might be due to dilution of the patient's blood with platelet-poor banked blood. Jackson, Krevans, and Conley[7] further showed that, in normal dogs receiving transfusions of platelet-deficient blood, the fall in the dog's circulating platelet levels could probably be accounted for on the basis of dilution alone.

At present, those studying the hemorrhagic diathesis associated with massive blood transfusions are faced with two problems relative to the role of platelets in this condition. First, what is the mechanism of production of this thrombocytopenia? Second, is the thrombocytopenia seen in this condition the etiologic agent for the abnormal bleeding? This paper presents the results of a study of the platelet levels in 41 patients receiving massive transfusion and a consideration of the questions posed.

MATERIALS AND METHODS

All blood samples were obtained through venipuncture with the use of siliconized syringes. Nine parts of blood were immediately placed into siliconized test tubes containing one part 3.8 per cent sodium citrate. The citrated blood was drawn up to the 0.05 mark of a siliconized R.B.C. pipette and the remainder of the pipette was then filled with 1 per cent Sequestrene, Na_2 solution made isotonic with sodium chloride. The pipette was shaken in a mechanical vibrator, and the platelet count was made using a standard counting chamber and conventional light microscope. All platelet counts were started within 15 minutes after sampling.

Forty-one patients undergoing heart surgery were studied. Thirty-five of these patients underwent open heart procedures with the use of a heart-lung

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machine (Sigmamotor pump and bubble-type oxygenator). The blood given these patients consisted of fresh (less than 18 hours old) heparinized blood (3 to 5 units) and A.C.D. banked blood which was usually less than 14 days old. Eight patients studied underwent closed heart procedures and these received only A.C.D. banked blood. A patient was considered to have abnormal bleeding if he demonstrated excessive oozing at the incision site or exposed pleural or pericardial surfaces despite adequate mechanical hemostasis. The differentiation between bleeder and nonbleeder was also made on the basis of excess loss of blood via the thoracotomy drain tubes postoperatively requiring transfusion volumes in excess of those characteristic to the procedure involved. Excluded from the category of "bleeders" were those patients whose blood loss was subsequently shown to be due to gross mechanical causes such as unligated vessels and the like.

In the open heart patients both the bleeders and the nonbleeders were kept on the heart-lung machine similar lengths of time and the distribution of cardiac lesions was similar in both groups. Heparinized blood (1,500 to 2,500 c.c.) was given these patients via mixture with the blood in the heart-lung machine during the operation. The remaining volume of blood administered was given intravenously.

RESULTS

Table I, *A*, shows the analysis of platelet counts on 8 patients who showed abnormal bleeding either during the time of surgery or within 5 hours postoperatively. The preoperative platelet counts are given as well as those of the 2- to 5-hour postoperative period. These latter figures represent platelet counts taken within a few hours of the time the patient was declared to be a bleeder. The maximum per cent drop in platelets explainable by dilution alone was determined by assuming that all transfused blood contained no platelets capable of circulating in the patient at the time of the 2- to 5-hour postoperative sample, estimating the patients circulating blood volume from the patient's weight according to Berlin,[1] expressing the volume of transfused blood in terms of the patient's blood volume and applying the equation of Wiener and Wexler[14] to determine the degree of dilution.

The average preoperative platelet count was 240,000/mm.^{3} and the average 2- to 5-hour postoperative platelet count was 112,000/mm.^{3} The average observed drop during the operative and early postoperative period was therefore 57 per cent. The maximum drop explainable by dilution alone was 80 per cent, or 23 per cent more than that actually observed. The lowest platelet count in this series was 60,000/mm.^{3} in experiment 62.

Table I, *B*, shows the platelet counts taken at the time abnormal bleeding was first noted in 8 patients undergoing closed heart surgery. Their average platelet count was 107,000/mm.^{3} and the lowest platelet count noted in this series was 55,000/mm.^{3} in experiment 55.

Table II shows the same categories described for Table I, *A*, but the patients in this series were patients who underwent open heart surgery, received massive blood transfusions, but did not show any evidences of abnormal bleeding. In this series the average preoperative platelet count was 220,000/mm.^{3} The

observed platelet drop during the operative and early postoperative period was 43 per cent, while the calculated maximum per cent drop in platelets due to dilution was 69 per cent. The lowest platelet count in this series was 55,000 /mm.^{3} in experiment 61.

TABLE I. PATIENTS EXHIBITING ABNORMAL BLEEDING MANIFESTATIONS

A. HEART-LUNG MACHINE PATIENTS

EXPERIMENT NUMBER	PREOP. PLATELET COUNT × 10^3	TOTAL VOLUME BLOOD GIVEN UP TO 2-HR. POSTOP. PERIOD (C.C.)	2-HR. POSTOP. PLATELET COUNT × 10^3	CALCULATED PER CENT DROP: 100 − 2-HR. POSTOP. PLATELET COUNT ÷ PREOP. PLATELET COUNT × 100 (%)	MAXIMUM PER CENT DROP BY 2-HR. POSTOP. EXPLAINABLE BY DILUTION (%)
5	257	4,000	188	37	56
17	243	6,000	90	63	63
23	252	7,500	90	65	76
24	75	11,000	81	--	89
33	455	8,500	172	--	--
50	230	8,500	95	59	89
62	160	13,500	60	63	95
68	250	9,500	120	52	95
Average	240	9,000	112	57	80

B. PATIENTS UNDERGOING CLOSED HEART SURGERY

EXPERIMENT NUMBER	51	54	55	56	63B	63A	63C	71A	AVERAGE
Platelet count at time bleeding noted × 10^3	63	74	55	144	100	177	120	120	107

TABLE II. PATIENTS NOT EXHIBITING ABNORMAL BLEEDING MANIFESTATIONS

EXPERIMENT NUMBER	PREOP. PLATELET COUNT × 10^3	TOTAL VOLUME OF BLOOD GIVEN UP TO 2-HR. POSTOP. PERIOD (C.C.)	2-HR. POSTOP. PLATELET COUNT × 10^3	CALCULATED PER CENT DROP: 100 − 2-HR. POSTOP. PLATELET COUNT ÷ PREOP. PLATELET COUNT −1 × 100 (%)	MAXIMUM PER CENT DROP IN PLATELETS BY 2-HR. POSTOP. EXPLAINABLE BY DILUTION (%)
9	193	5,000	73	62	63
13	300	3,700	113	--	--
35	167	4,000	111	--	--
36	278	7,500	148	--	--
38	400	6,100	188	53	70
39	366	5,100	144	61	83
41	155	6,000	122	32	70
42	230	5,500	102	56	74
43	157	7,000	100	36	84
44	160	4,000	88	45	56
45	266	3,000	158	41	67
46	200	3,000	95	52	46
47	240	4,000	75	69	72
48	210	2,600	144	31	46
49	288	3,500	166	43	46
58	122	3,000	110	10	56
59	210	7,500	130	38	80
60	221	7,250	125	43	97
61	160	8,000	55	66	77
63	210	5,600	155	26	60
64	130	4,500	110	16	68
65	200	7,000	120	40	78
66	190	9,000	90	53	83
69	240	8,000	160	33	81
70	210	7,500	120	--	--
Average	220	5,200	120	43	69

DISCUSSION

In most patients of this series who showed abnormal bleeding tendencies, an associated thrombocytopenia was noted. However, a control series consisting of patients who received similar volumes of blood, underwent similar operative procedures, and did not show evidences of abnormal bleeding had an almost identical degree of thrombocytopenia. This indicates that thrombocytopenia alone is not sufficient to account for the abnormal bleeding seen in these patients. Since several of the patients who bled had platelet counts well within the normal range (experiments 5, 33, 63A), it is also questionable whether a thrombocytopenia is necessary for the production of the abnormal bleeding in some of the patients studied. Inasmuch as the low platelet counts seen in these patients were neither sufficient nor necessary for the production of abnormal bleeding, it seems evident that thrombocytopenia cannot be incriminated as the sole cause for the hemorrhagic diathesis.

In all cases studied the maximum per cent fall in platelets which could be explained on the basis of dilution alone was greater than the observed platelet drop during the operative and early postoperative period. This may have been due to the fact that the calculated blood volumes of the patients may have been lower than the patient's actual blood volume; the patient may have been supplementing his circulating platelet levels with platelets released from their stores in the body. Most important, however, is the fact that in calculating the maximum per cent fall accountable for by dilution it was assumed that the donor blood contained no platelets capable of circulating in the recipient patient. This assumption has been further treated elsewhere in connection with thrombocytopenia following the use of the heart-lung machine.[6]

It is noteworthy that the role of thrombocytopenia in the production of any abnormal bleeding tendency has not been established. When Duke[4] first reported on patients with a hemorrhagic diathesis who also had a low platelet count, he pointed out that the evidence for the latter as being the cause for the former was purely circumstantial. More recent investigations in dogs[2, 15] have shown that simple thrombocytopenia was not in itself sufficient to produce a hemorrhagic diathesis. In their study of leukemic children, Freeman and Hyde have pointed out that "thrombocytopenia, per se, appears not to be a completely adequate cause of bleeding. This view is supported by the presence of 36 instances of critical thrombocytopenia in which there was no evidence of bleeding."[5] Spaet,[12] in his excellent review of the literature, has remarked on the frequent lack of correlation between platelet values and purpuric and petechial manifestations of abnormal bleeding. It would appear, therefore, that at present one may be hesitant to place the onus on simple thrombocytopenia as the etiology of abnormal bleeding, in cases where the only abnormal finding noted is a low platelet count.

CONCLUSIONS

1. Evidence has been presented which indicates that simple thrombocytopenia *is not* the cause for the abnormal bleeding following massive transfusions in the patients studied. However, it is possible that the low platelet counts might have been contributory in producing the hemorrhagic diathesis observed.

2. A large part of the thrombocytopenia seen in the patients studied was probably due to dilution of the patients' blood with platelet-poor banked blood.

3. Note was made of the difficulty in establishing simple thrombocytopenia as the cause of any abnormal bleeding tendency.

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STUDIES ON THE CAROTID SINUS WITH REFERENCE TO THE SYNDROME OF LUDWIG'S ANGINA

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IN THE literature pertaining to the syndrome of Ludwig's angina references are found to the role of the carotid sinus (Fig. 1) in the production of dyspnea and terminal respiratory failure sometimes seen in patients suffering from this disease.[1-3] While it is generally agreed that mechanical blockage of the air passages occurs, the view has been expressed that in the presence of a Ludwig's induration the carotid sinus is hyperirritable and that pressure exerted on this organ by the phlegmonous mass may induce a fatal apnea.

The principal experimental evidence in favor of this hypothesis is due to Weese,[3] who produced suppurative indurations in dogs by injection of turpentine over one of the carotid sinuses. He found that pressure applied over the affected sinus could produce apnea under conditions of light barbiturate anesthesia, but apnea could not be induced by pressure applied to the opposite unaffected carotid sinus. Pressure over either sinus produced no apnea when the anesthesia was deepened. This he felt was due to paralysis of the carotid sinus mechanism by the anesthetic.

Since the clinical experience of one of us (H. H. W.) in 17 patients (1925 to 1958) with classic angina Ludovici (Fig. 2) (secondary to dental pathology) makes it appear doubtful that the respiratory disturbances seen in cases of Ludwig's angina can be ascribed to carotid sinus effects, we have reinvestigated in dogs the respiratory regulating abilities of the carotid sinus using both the surgically isolated carotid sinus and Weese's preparation.

METHODS

Two groups of dogs were used. In the first group of 3 animals, the effects on the respiration due to varying the pressure on the surgically isolated carotid sinus were studied. Each animal was prepared as follows. Anesthesia was induced by the intraperitoneal injection of 25 mg. of sodium pentobarbital per kilogram of body weight and a femoral artery was cannulated for the recording of blood pressure. The opposite femoral vein was isolated to be available for intravenous injections as required. An endotracheal tube was inserted and connected to a tambour for the recording of the respiratory rate. A midline incision was made in the neck and the common carotid arteries were located by blunt dissection. These vessels were followed to their bifurcation and loose ligatures

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were placed around the internal and external carotids just above carotid sinuses. Ligatures were also placed around the common carotids below the sinuses. Thus by applying tension to the proper ligatures pressures in the carotid sinuses could be increased or decreased at will. After the operative procedures were

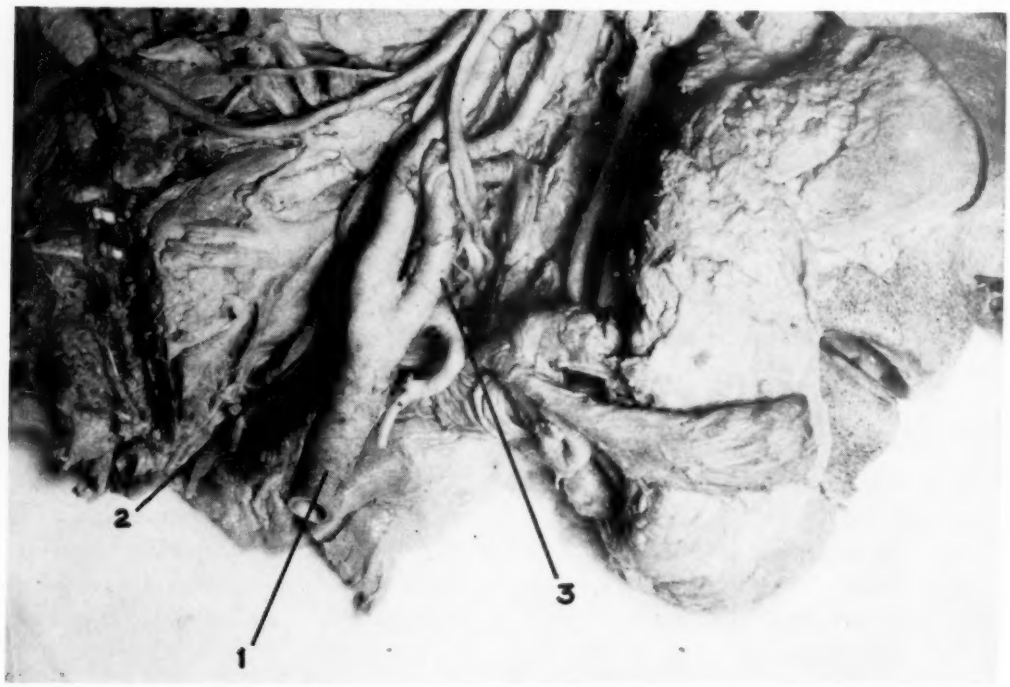

Fig. 1.—The carotid sinus (*2*) is a bulbous dilatation at the bifurcation of the common carotid artery. *1*, The common carotid artery. *3*, The internal carotid artery. (From original dissection by H. H. W.)

Fig. 2.—Ludwig's angina, secondary to dental pathology.

completed, the anesthesia was allowed to lighten and was maintained at a level just below the point at which the animal could make spontaneous limb movements.

The second group of 4 dogs was prepared in a manner similar to that of Weese. Each animal was given an injection of 0.5 ml. of rectified oil of turpentine over the right carotid sinus and was left overnight until the induration had "ripened." Anesthesia was then induced and the femoral vessels were prepared as above. The head and neck were undisturbed, the respiratory rate was determined by counting the respiratory fluctuations in the blood pressure. The effects of manual pressure on the carotid sinuses, affected or not by turpentine indurations, were observed at levels of anesthesia varying from a point at which there were shivering and response to pain to deep surgical anesthesia.

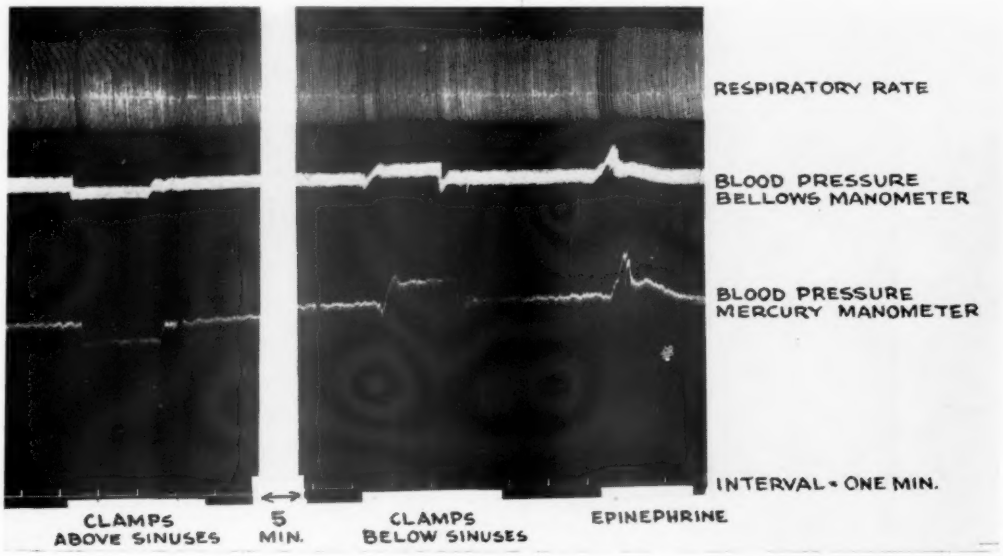

Fig. 3.—Changes in blood pressure and respiratory rate produced by pressure alterations in the surgically isolated carotid sinuses of a dog under light pentobarbital anesthesia.

RESULTS

Fig. 3 illustrates typical results obtained by increasing or decreasing the pressure in the surgically isolated carotid sinuses. The increase in pressure was achieved by tightening the ligatures which had previously been placed around the external and internal carotid arteries, the decrease by applying the same procedure to the ligatures around the common carotids. Increased pressure maintained for 2 minutes produced the expected fall in blood pressure and only a brief apnea, followed by recovery of the respiratory rate to the control level. Decreased pressure resulted in a rise in blood pressure and some decrease in respiratory rate but no apnea. The classic apnea following a pressor dose of epinephrine and the typical blood pressure changes due to pressure variations in the sinuses testify to the intactness of the nerve connections of the carotid sinus with the central nervous system. These results were repeated many times

on each of 3 animals at varying levels of anesthesia, and prolonged apnea was never observed. Instead, an increase in respiratory rate was the more common finding. Thus although the trauma incident to surgical isolation of the carotid sinuses might be expected to produce hypersensitivity of these organs, we were unable to induce a prolonged apnea when the anesthesia was light; nor could we demonstrate a paralysis of the carotid sinus mechanism under deep anesthesia.

Fig. 4.—Phlegmonous infiltration floor of mouth and neck simulating classic angina Ludovici following injection with turpentine.

Of the 4 dogs injected with turpentine, two developed unilateral indurations which involved only the right carotid sinus, and in the other two the swelling spread over the midline of the neck and may possibly have involved the left carotid sinus. However, the results obtained by manual pressure applied over the organs were the same regardless of whether or not the induration involved the sinus. The lesions, illustrated in Figs. 4 and 5, were uniformly

Fig. 5.—A typical lesion produced by the injection of 0.5 ml. of rectified oil of turpentine over the right carotid sinus.

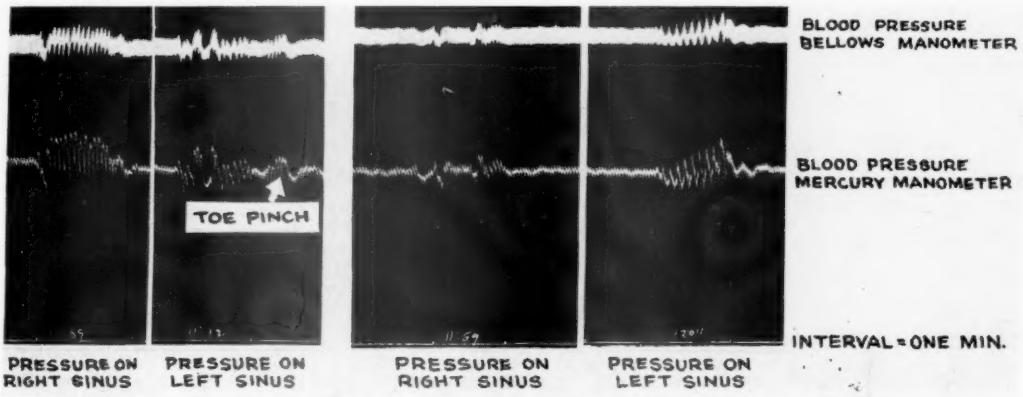

Fig. 6.—Changes in blood pressure and respiration (read from blood pressure tracing) produced by manual pressure on the carotid sinuses of a dog in which a turpentine lesion had been produced over the right carotid sinus. Left tracing, light anesthesia; right tracing, deep anesthesia.

edematous, suppurative, and relatively bloodless. Fig. 6 illustrates the findings obtained when pressure was applied for one minute to the right sinus definitely involved by the lesion and to the left sinus of the same dog which was not involved by the lesion. The records at 11:09 and 11:12 were made under very light anesthesia as evidenced by the pain response elicited when the animal was pinched between the toe pads. The records at 11:59 and 12:04 were taken under deep anesthesia, evidenced by the disappearance of the corneal reflex and relaxation of skeletal muscle. The head and neck were undisturbed except for the application of pressure, and respiratory changes were recorded as fluctuations in the blood pressure. It is apparent that the only changes observed were a decrease in the respiratory rate compensated by an increased depth of respiration and a moderate increase in blood pressure regardless of the depth of anesthesia. Since pressure had to be applied by placing the hand over the general area of the carotid sinus, we believe that slight variations in response were due to differences in positioning of the investigator's hand or to the amount of pressure applied. Again, the findings illustrated were repeated many times on each of 4 dogs at varying levels of anesthesia and neither apnea nor paralysis of the carotid sinuses was ever demonstrated.

CONCLUSIONS

Our findings do not substantiate the view that pressure on a carotid sinus involved in an induration similar in anatomic and clinical appearance to that of Ludwig's angina could produce an apnea of sufficient duration to be fatal.

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A PLASTIC PROSTHESIS FOR PALLIATING CARCINOMA OF THE ESOPHAGUS

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FOLLOWING a study based on 100 cases and 18 postmortem examinations, Souttar,[10] in 1927, recognized the futility of jejunostomy and gastrostomy for inoperable or unresectable carcinoma of the esophagus. Convinced that palliation rather than cure was indicated in such cases, he designed a tube for peroral introduction through the obstructed portion of the esophagus. His tube was flexible, made of rubber, and surrounded by German silver wire. It was oval in cross section; the upper end was funnel shaped. He introduced this tube through an esophagoscope after dilation of the channel through the growth with a bougie. Fig. 1 shows the instruments used to introduce the tube. Fig. 2 shows the tube in position. This procedure never became popular. A probable explanation was the real danger of perforation or rupture of the esophagus during dilation. This method was again introduced by Allison[1] in 1949 after roundly condemning jejunostomy and gastrostomy.

As anesthesia and thoracic surgery progressed, other surgeons designed tubes and introduced them during transthoracic operations, either after exploration or definitively. Mackler and Mayer,[7] in 1954, introduced "an indwelling tube inserted at the time of thoracic exploration when resection was not feasible." The tube (Fig. 3) was inserted through a longitudinal incision 2 inches above the lesion after graduated dilators were passed to enlarge the channel to the greatest possible width. Mortality of this series was 31.5 per cent. The complications encountered were fistula formation and empyema, passage of the tube into the stomach, vomiting of the tube, and obstruction due to impaction of food within the tube. Esophageal fistula, empyema, and passage of the tube into the stomach all occurred in one case. In 35 cases the survival period averaged 3.4 months. In comparison, the average survival period following thoracic exploration for unresectable carcinoma of the esophagus is 1.7 months, as computed by Wu and Loucks.[11]

Ravitch and Bahnson[9] reported the insertion of a plastic tube during operation when resection was not feasible. The tube was a variant of the Souttar tube forced into the malignant stricture by pressure on a removable obturator. Ravitch and Bahnson state, "Survival and cure rates are so rare it seems justifiable to direct our efforts to palliation rather than cure and to seek methods which will yield the best return in terms of patient comfort with deglutition restored."[9]

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Brown,[2] in 1949, used a silver tube, flanged at one end. He inserted it through a slit below the lesion, with the flange directed caudally. He placed a ligature of cellophane about the esophagus, below the distal flanged end

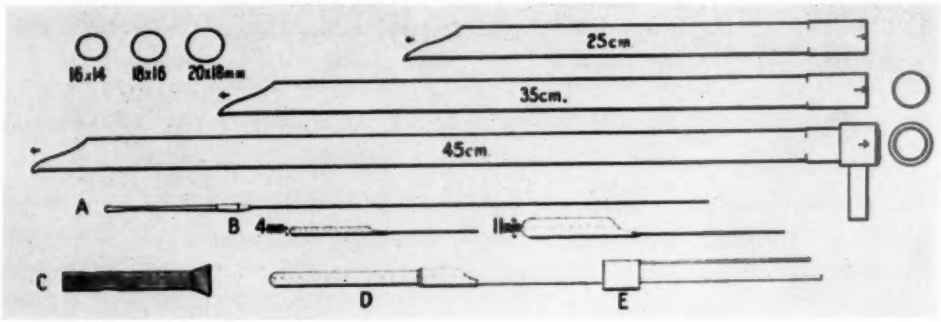


Fig. 1.—Special esophagoscopes and instruments used by Souttar for intubation. *A*, Flexible bougie. *B*, Aluminum dilators to pass over shaft of *A*. *C*, Flexible wire tube. *D* and E, Introducer and releasing ring.

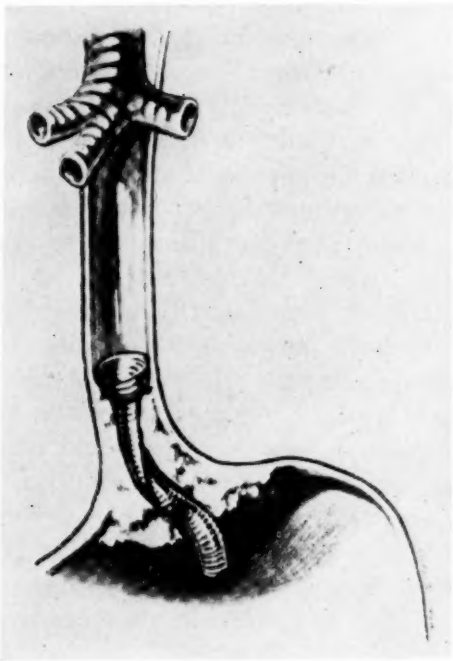


Fig. 2.

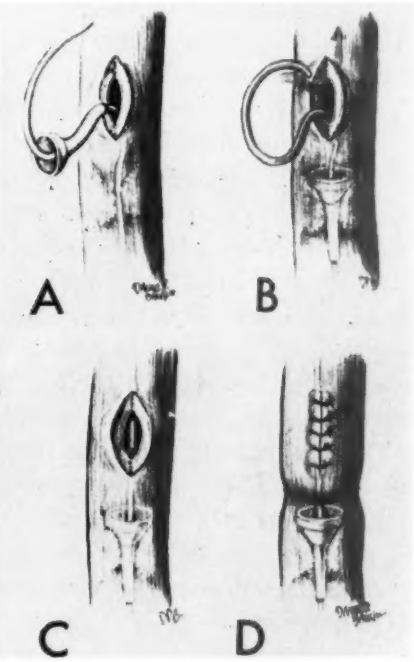


Fig. 3.

Fig. 2.—Souttar's tube through malignant stricture of lower esophagus.

Fig. 3.—Tube and operative technique of Mackler and Mayer. *A*, Esophagotomy and Levin tube, with prosthesis threaded on it, passed through the carcinoma toward the stomach. *B*, The prosthesis passed through the obstruction. The cuff rests upon the growth. *C*, The proximal end of the Levin tube has been passed toward the mouth. *D*, The esophagotomy has been closed. An extramural periesophageal ligature has been placed above the level of the cuff of the tube to prevent emesis of the tube.

of the tube, slightly constricting the esophagus at this point to form a shelf which kept the tube from falling down toward the stomach. The flange kept it from passing upward into the buccal cavity.

Coyas[4, 5] reports the use of a tube of "plastic material (polyvinyl chloride and 35 per cent other plastic material). Thermolabile at body temperature, it is remolded by the shape of the tumor . . . which holds it tightly within the stenosis." A bougie was used both for exploring and dilating. The tube was inserted under general anesthesia. Results in 16 cases were as follows: In 3 cases the stenosis was too great. In one case esophagoscopy was not possible because of an aortic aneurysm. Intubation was possible in 12 patients. The average length of survival, excluding one patient who died on the fourteenth day, was 3 months. Three patients were still living after 3½ months. A secondary perforation and esophageal fistula were discovered by radiography on the second postoperative day in a patient aged 72 years. In 2 cases the tube slipped and was passed by rectum. Obstruction of the tube occurred in 2 cases: one patient swallowed too large a piece of meat, and in another patient the tumor grew into the lumen of the tube.

Compare these results to the statistics reported by Meyer and Kozol.[8] In a review of 80 patients who had gastrostomy, 43 cases died within 2 months.

Cooper and Buxton[3] in 1948, reporting 199 cases of gastrostomy, made the following observations:

1. No significant extension of life has been gained for these patients.
2. Thirty per cent had one or more complications associated with gastrostomy.
3. The majority had actual discomfort, minimal palliation, and removed tubes wilfully.
4. A satisfactory state of nutrition was brought about only when the patients were esophagectomized and an artificial or surgically reconstructed esophagus was made.

Survey of the literature since Souttar (1927) indicates that all authors using peroral route and those intubating during thoracotomy, with the exception of Brown, used flexible tubes, that all tubes, including Brown's, are inserted into previously dilated channels, and that there is occasional perforation and frequent regurgitation or passage of the tubes into the stomach. I am convinced that dilation of the lumen through the growth prevents a snug fit of the prosthesis and that a flexible tube placed in a dilated channel (lumen) is more likely to pass through that channel or to be regurgitated.

To avoid likely insecurity of the tube position, perforation during dilation, and the risks associated with a thoracic approach in inoperable, unresectable carcinoma in debilitated patients, I have designed and developed a rigid tube for peroral insertion. Its passage without previous dilation is through the growth in line with the remains of the esophageal channel. Its screw-shaped exterior allows for a perfectly snug fit. The insertion may be done under general or topical anesthesia.

The tube, fashioned in the form of a hollow screw, is machined from a nylon rod. The thread of the screw has a horizontal shoulder which is perpendicular to the axis of the tube (*C* in Figs. 4, 5, and 6). This shoulder

prevents the regurgitation of the tube. The external diameter of the tube is limited by the internal diameter of the esophagoscope. We use a Lynah scope, the lumen of which is 10 mm. in its short diameter. The diameter of the channel of the screw tube is 8 mm. The upper end of the screw thread is rimmed.

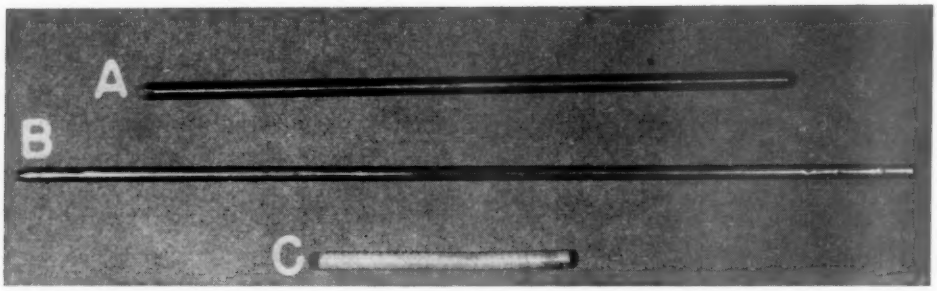


Fig. 4.—*C* is a hollow tube whose exterior is fashioned as a screw, with L-shaped notches on opposite sides of the rim at one end. *B* is a hollow "screw driver" with knurls opposite each other near the end. *A* is the release tube. It is made to fit over *B*. It has slots at the lower end which fit over the knurls on *B*. Its function is to enable *B* to be withdrawn from *C*.

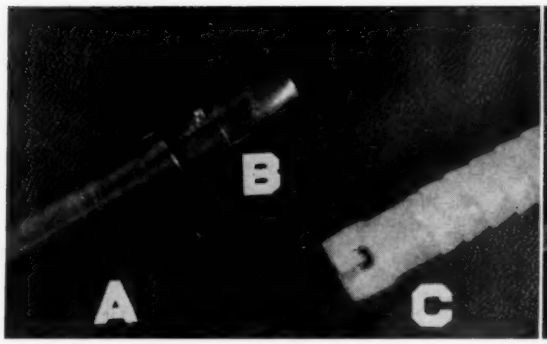


Fig. 5.

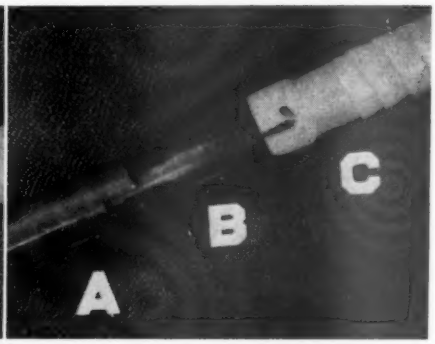


Fig. 6.

Fig. 5.—The functioning ends of *C*, *A*, and *B* in detail.

Fig. 6.—*B* is fitted into *C*, with the knurls in the notches. *A* is already slid over *B*. With a turn of *B* clockwise and *A* slid toward *C* so that the slots on *A* engage the knurls on *B*, *C* is disengaged and pushed free. In other words, *B* is freed and can be withdrawn from *C* and thus from the esophagus.

Through the upper portion of the tube (the rim), two L-shaped notches are cut on opposite sides(*C* in Figs. 5 and 6). It is through these notches that the propulsion or removal of the tube through the growth is applied by means of a hollow metal rod or so-called "screw driver" (*B* in Figs. 4, 5, and 6). The lower end of the hollow screw driver, for 2 cm., is ground to fit the interior of the screw tube. One centimeter above the lower end of this hollow driver, on opposite sides, there are knurls, 2 mm. in diameter (*B* in Figs. 5 and 6). These knurls, or knobs, engage the L-shaped notches when the hollow driver is introduced into the screw tube (*B* in Figs. 5 and 6). Fig. 6 shows the fit of the screw driver into the tube ready for propulsion which is obtained by turning in a clockwise direction. Removal of the tube is accomplished by turning in counterclockwise direction. The knobs are brought midway in the

notch for disengagement. Should a bend in the esophagus prevent disengagement, a release tube is slid down over the driver (Fig. 5, *A*), which pushes the screw tube off the driver (Fig. 6, *A*).

Before the passage of the tube is undertaken study must be made of the patient's esophagram to determine the length of the occluded portion of the esophagus. It is to be remembered that the occluded portion which is due to circumferential growth does not actually extend longitudinally as far as the growth defect in the x-ray plate indicates. The prosthesis must pass through the occluded segment only. It should not project more than 1 cm. above the occlusion. X-ray exaggerates the length of the lesion by about 20 to 25 per cent. This must be taken into account in determining the length of the prosthesis necessary.

PREPARATION OF THE PATIENT

Sedation.—The patient is given suitable preanesthesia sedation.

Anesthesia.—The operation may be done under topical or general anesthesia with intratracheal intubation.

X-ray Examination.—Arrangements are made for x-ray examination on the operating table, during and following the intubation.

Esophagoscopy.—Esophagoscopy is performed according to the method described by Chevalier Jackson.[6] We have found the Lynah esophagoscope satisfactory for our purpose.

When the growth comes into view, a biopsy is taken. Under direct vision, a No. 10 Jackson bougie is passed, guiding the tip into what remains of the esophageal lumen. Because it is undesirable to force the passage it is better that a small-sized bougie be selected so that the remains of the lumen will not be dilated. By withdrawal of the bougie partially, one can feel the lower end of the constricting growth when the shoulder of the bougie encounters the lesion. This aids in determining the actual length of the obstruction and of the required prosthesis. The screw tube with the stem ("driver") attached is then passed and threaded over the wire of the bougie until the lower end of the screw tube engages the growth. At this point a mark is made on the meter scale on the stem of the driver at a level of the orifice of the esophagoscope. To this is added the length of the occlusion as determined by previous study of the esophagram and information obtained when the bougie was passed. Another mark placed on the stem toward the outer end will be the limit of the introduction of the tube. By slow clockwise turning of the stem and gentle push (pressure) caudalward, the tube reams its way through the growth until the prearranged scale mark on the "driver" reaches the opening of the esophagoscope. The bougie is then withdrawn. With the screw driver still attached to the tube, a rubber tube is attached to the outer end of the screw driver, barium is passed through the tube in sufficient amount to pass into the stomach, and an x-ray is taken. If the x-ray shows the tube properly placed, the "driver" is disengaged from the

tube by turning it several degrees to the left and is withdrawn. If the tube is passed too far down or not far enough, the position of the tube may be altered by turning the "screw driver" clockwise or counterclockwise. To prevent ulceration and perforation by the tube, the latter's end should not extend more than 1 cm. above the obstructing portion of the carcinoma.

CASE REPORTS

CASE 1.—B. M., a 60-year-old white woman, was admitted Jan. 18, 1956. Her complaint was choking and inability to swallow. Her illness began 6 months prior with inability to swallow solids, then soft foods, and finally liquids. For the last 2 weeks obstruction was complete. She lost 48 pounds. Physical examination showed a poorly developed, emaciated woman, weighing 72 pounds. There was a large stony nontender mass in the left supraclavicular fossa. X-ray showed a kyphoscoliosis of the dorsal spine. Esophagram, Jan. 19, 1956, showed a long, irregular destructive lesion of the mid-segment of the esophagus compatible with the presence of a carcinoma (Fig. 7, *A* and *B*). On Feb. 2, 1956, an esophagoscopic examination revealed a fungating mass projecting into the lumen of the esophagus. A biopsy was taken and reported to be squamous cell carcinoma. At this operation a Jackson bougie was passed through the lumen of the mass and, using this as a guide, a nylon plastic tube was screwed through the growth creating a channel. The patency of this channel was verified by the passage of a barium suspension through it (Fig. 7, *C*). The patient began to take semisolid food in 6 hours. She was discharged from the hospital Feb. 7, 1956. She returned to work promptly and continued to improve, gaining 22 pounds. She was re-admitted to the hospital on Sept. 21, 1956, 7 months and 19 days after her first operation, complaining of pain at the root of her neck, difficulty in swallowing, and weakness. Esophagram the following day revealed dilatation of the upper third of the esophagus and showed the plastic tube in place below. Barium passed through and around the tube into the stomach. Following the esophagram the patient had an irregular fever to 102° F. X-ray of the chest revealed fluid at the left base. After subsidence of the fever, the patient was esophagoscoped, and the tube was removed and replaced with a longer one. X-ray showed that the barium flowed freely through the tube into the stomach. Following the operation the patient was able to swallow but suffered greatly from anorexia. She went downhill rapidly and expired on Oct. 10, 1956. The survival period following insertion of the tube was 8 months, 10 days. A postmortem examination was performed.

Anatomic Diagnosis.—The findings were: squamous cell carcinoma of esophagus with extension into cardia of stomach, left main bronchus, left lower lobe of lung, pericardium, left lower lobe of pulmonary vein with metastases to left supraclavicular, tracheobronchial, hilar, mediastinal, perigastric, pericholedochal, peripancreatic, periaortic, and mesenteric lymph nodes. There were also perforations (2) of the esophagus into left and right pleural cavities, not traumatic. Esophagopleuropulmonary fistulas with abscess formation and left lower lobe and right upper lobe aspiration pneumonia of all lobes of the lungs were seen. Fig. 7, *D* is a photograph of the specimen removed at autopsy. The esophagus is incised lengthwise with the prosthesis in situ. A clamp and a probe may be seen in the sinus tract.

CASE 2.—P. W., a 70-year-old white man, was admitted Sept. 10, 1956, complaining of cough of 5 months' duration and difficulty with swallowing. A destructive lesion in the esophagus and fluid in the right chest had been demonstrated by x-ray prior to admission (Fig. 8, *A*). In the hospital, cytologic examination of this fluid revealed the presence of groups of tumor cells. Postparacentesis x-ray of the chest showed infiltration above the fluid level, probably extending from a metastatic process. Following a course of x-ray therapy in the hospital he was discharged on Sept. 25, 1956. The diagnosis was "carcinoma of esophagus with metastases." The patient was readmitted to the hospital on Nov. 6, 1956, because of inability to swallow. On Nov. 10, 1956, during esophagoscopy,

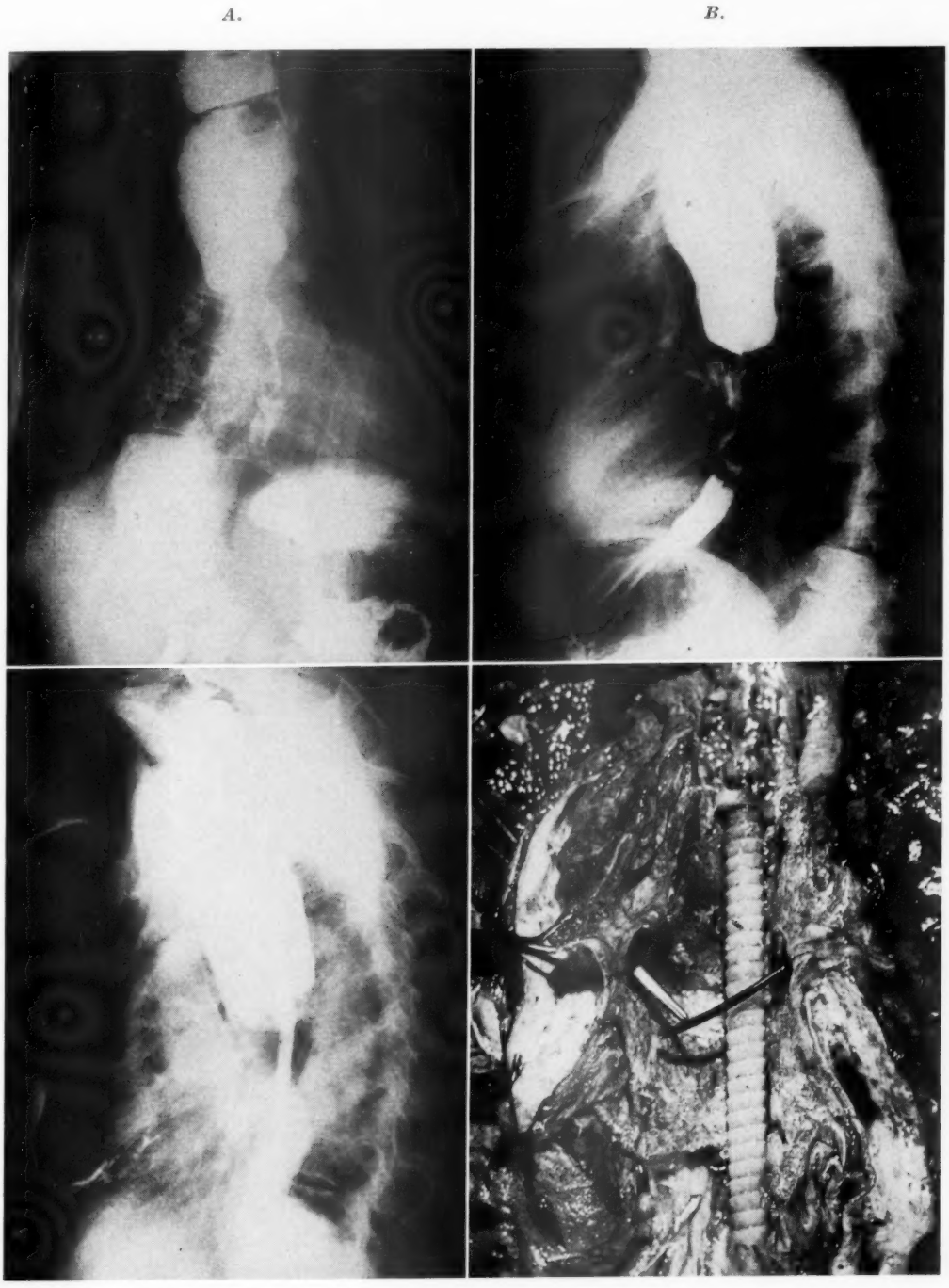
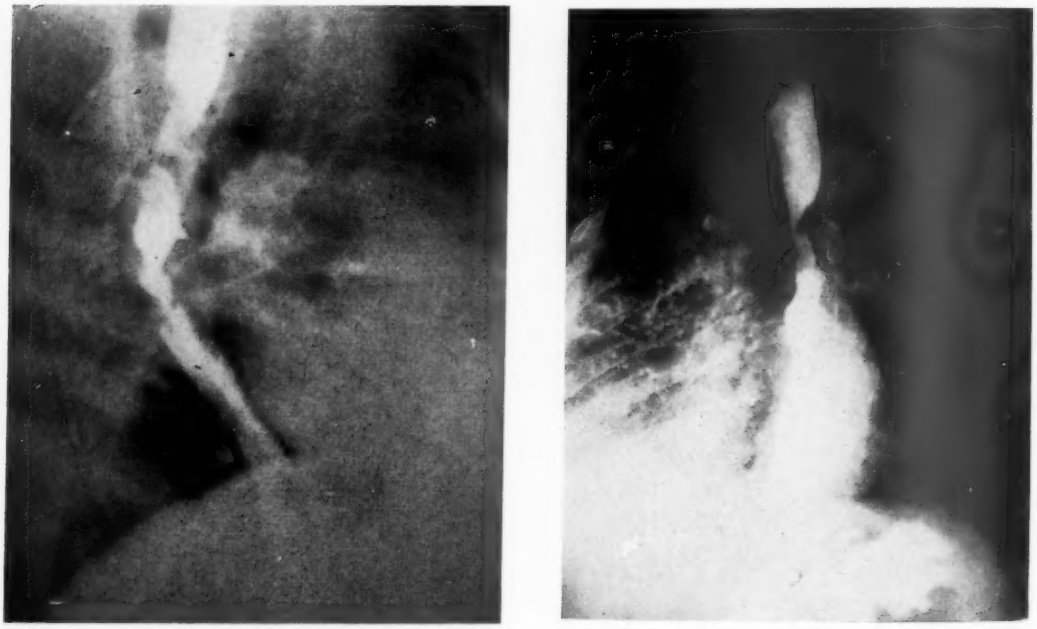


Fig. 7.—Case 1. *A*, Anteroposterior esophagram. *B*, Lateral view esophagram. *C*, Esophagram showing patency following insertion of prosthesis. *D*, Specimen of esophagus and lungs removed at postmorten examination. The tube is in situ. It measures 14.5 cm. in length. The instruments show the canalization of the growth through the bronchus and lungs.

a biopsy was taken and a plastic tube was placed in the growth, creating a channel through it. X-ray taken subsequent to the placement of the tube showed the barium to flow freely through the tube in the mid-esophagus into the stomach (Fig. 8, *B*). The patient took soft and solid foods promptly and very well. He was discharged from the hospital on Nov. 19, 1956. The patient was readmitted to the hospital on Dec. 11, 1956, having done quite well until the day prior to admission when he had difficulty in swallowing and slight hematemesis. On Dec. 14, 1956, during esophagoscopy, the tube was replaced with a somewhat longer one. An x-ray taken at the time revealed that the barium flowed freely through the tube in the middle third of the esophagus into the stomach. Following this he was able to eat a soft diet. He was discharged from the hospital on Jan. 16, 1957. Subsequent to his discharge from the hospital the patient was able to swallow with ease. He died suddenly at home on Jan. 23, 1957. Permission for postmortem examination was not obtained.

The patient's survival period following insertion of tube was 2 months, 14 days.



A. *B.*

Fig. 8.—Case 2. *A*, Esophagram showing carcinoma of the esophagus and fluid in the chest. *B*, Esophagram following the insertion of the prosthesis.

CASE 3.—F. B., a 53-year-old white woman, was admitted Oct. 29, 1956, complaining of inability to swallow. This difficulty began about 6 weeks earlier and was complete on admission. Attempts to eat caused pain in her neck and prompt vomiting. There was gradual but marked loss of weight.

On examination the patient appeared quite ill. There was marked wasting. Her blood pressure, pulse, respirations, serology, and blood chemistries were normal. Esophagram, Oct. 29, 1956, disclosed the presence of an infiltrative lesion of the esophagus at the level of D_4 to D_7 (Fig. 9, *A*). On Nov. 12, 1956, a polypoid, nonulcerative mass was seen in the upper third of the esophagus and a biopsy was taken. Pathologic examination of this material revealed a squamous cell carcinoma of the esophagus. On Nov. 23, 1956, with the patient under topical anesthesia, through an esophagoscope, a nylon plastic screw-type tube was inserted through the growth. Subsequent esophagrams showed that the barium flowed through the tube into the stomach and that the tube was in contact with the normal esophagus at the proximal and distal ends (Fig. 9, *B*). Within several hours the patient was able to swallow semisolid and chopped foods very well. She was discharged from the hospital on Nov. 30, 1956.

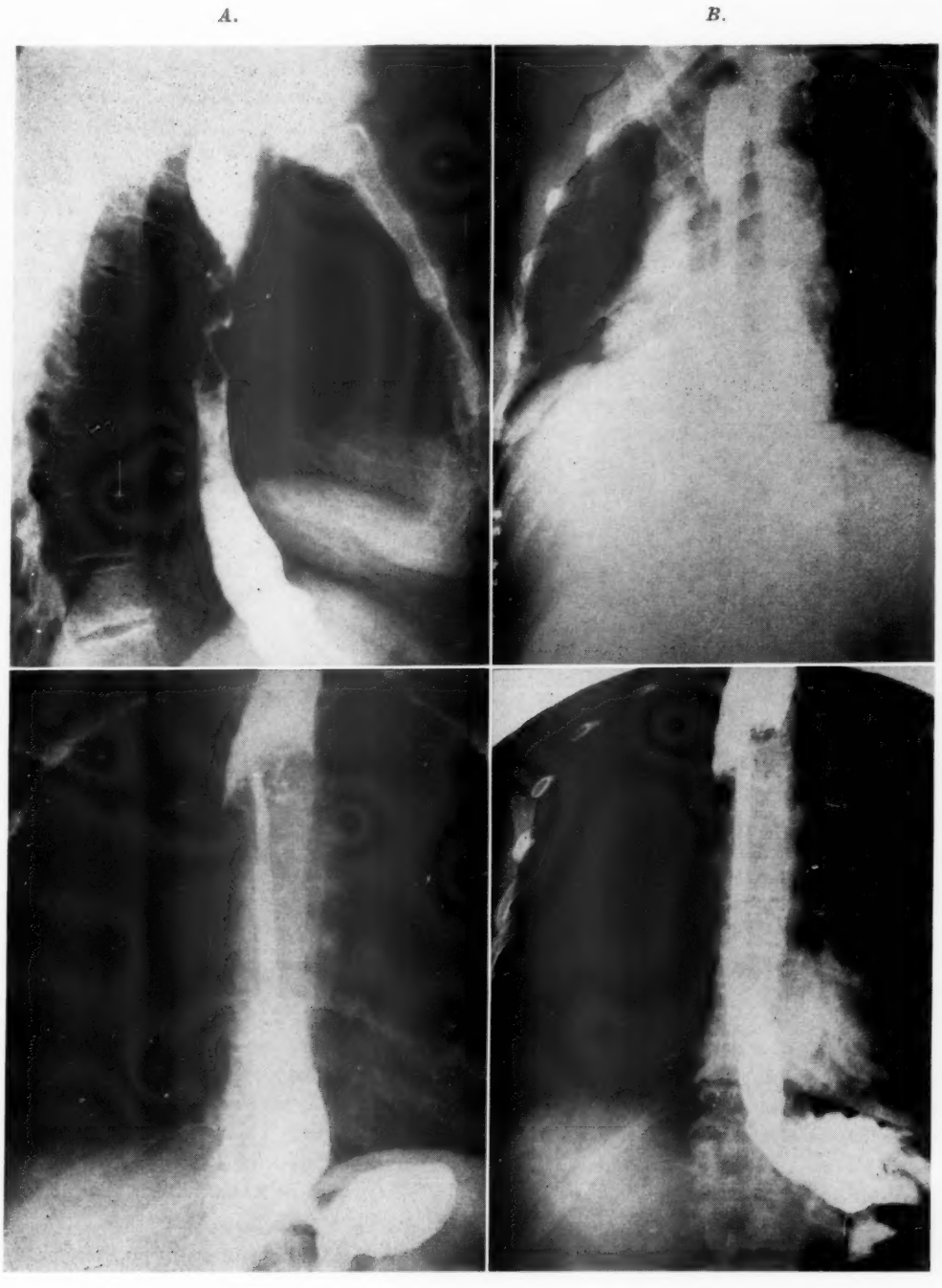


Fig. 9.—Case 3. *A*, Esophagram showing carcinoma of the esophagus. *B*, Esophagram following insertion of prosthesis, Nov. 24, 1956. *C*, Esophagram, Jan. 21, 1957, showing prosthesis in place after removing overgrowth and adjustment of the tube by screwing it in an upward direction. *D*, Esophagram, March 11, 1957. The prosthesis is still functioning 7 weeks since its last adjustment, Jan. 21, 1957.

The patient returned on Dec. 13, 1956, with the complaint of regurgitation of food. She suggested that her disability was due to fear. Esophagram the day of admission revealed no evidence of obstruction. The barium passed through the plastic tube into the stomach. On the fourth hospital day, the patient swallowed liquids well. On the sixth day she developed fever and cough. X-ray showed pneumonitis. On the thirty-sixth hospital day, Jan. 19, 1957, her esophagus became obstructed. On the thirty-eighth hospital day, with the patient under topical anesthesia, an esophagoscopic examination was done and the plastic tube was readjusted by screwing it upward, following the removal of the malignant tissue overhanging the proximal end of the tube (Fig. 9, *C*). The elevated position of the tube was verified by esophagram. The patient was discharged on the forty-seventh day, able to swallow semisolid and chopped foods well.

She returned to the hospital on March 5, 1957, complaining of severe cough and increasing weakness. X-ray of the chest on admission showed infiltration of the lower left lung. An esophagram (Fig. 9, *D*), March 11, 1957, showed no evidence of obstruction of the esophagus. On March 20, 1957, with the patient under topical anesthesia, bronchoscopy was performed and showed that immediately above the carina the lumen was constricted to a narrow slit, 2 mm. wide, due to external pressure from below. It was thought that the compression of the trachea was due to the esophageal neoplasm.

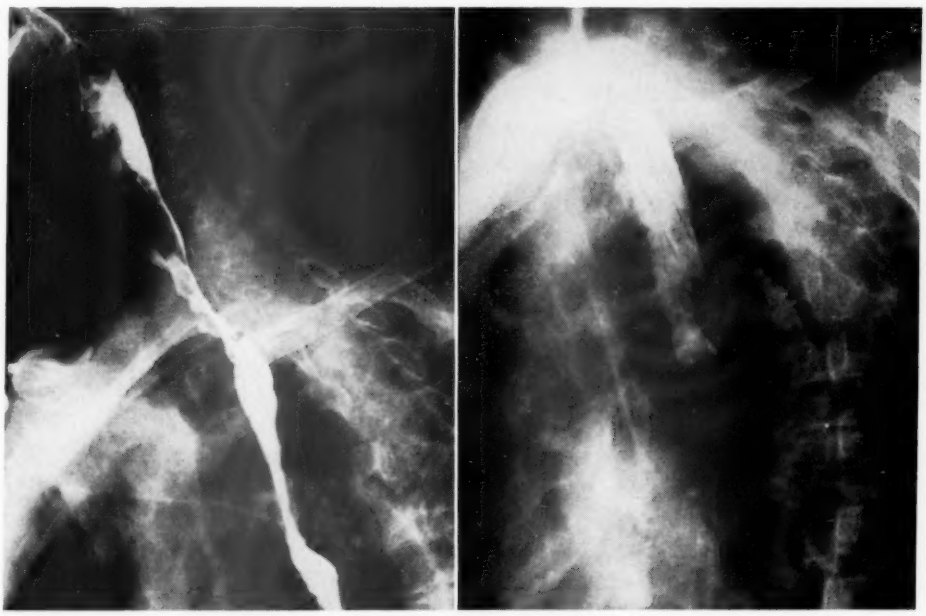
The patient continued to be in respiratory distress and to refuse food. In spite of treatment with a new alkylating drug,* the patient's course was progressively downhill. She expired on April 8, 1957. This patient's surival period following the insertion of the tube was 4 months and 15 days.

CASE 4.—O. S., a 71-year-old white man, was admitted May 23, 1957, complaining of inability to swallow. This difficulty began 7 weeks prior to admission, increasing in severity so that during the past 2 weeks he had even regurgitated liquids. The patient had lost 30 pounds in weight. Examination showed the patient to be poorly nourished and quite ill. There were several masses in the thyroid and along the left sternomastoid. The trachea was somewhat protuberant. Laboratory examinations were normal except for a secondary anemia. An esophagram showed the cervical esophagus to be obstructed by an annular contriction associated with mucosal irregularity. A biopsy taken at esophagoscopy on June 6, 1956, revealed an undifferentiated squamous cell carcinoma. Widespread metastases proved the growth to be inoperable. The patient was given a course of roentgen therapy and at the time of discharge on July 23, 1956, he was able to swallow. The patient was readmitted on Nov. 20, 1956, complaining of increasing difficulty in swallowing. He was unable to take even liquids. On Nov. 21, 1956, an esophagram revealed a tumor in the proximal esophagus, as in the original examination (Fig. 10, *A*). On Nov. 29, 1956, with the patient under sodium Pentothal and topical anesthesia, an esophagoscopy was done. A screw-type plastic tube was inserted through the neoplasm in the esophagus. An x-ray taken immediately showed the barium mix to flow freely into the stomach. An esophagram taken the following day showed the plastic tube in the esophagus and the proximal end of the tube to be slightly below the proximal end of the neoplasm. Therefore the plastic tube was manipulated into better position a few days later (Fig. 10, *B*). The patient was discharged on Dec. 12, 1956, able to take his food with ease.

He returned for admission 2 weeks later complaining of inability to swallow following the passage of his tube per rectum. Examination on this admission showed the patient to be chronically ill but in no acute distress. He had palpable anterior and posterior cervical nodes. Lungs revealed dullness to percussion and decreased breath sounds in the upper lobe. Repeat esophagrams revealed an extensive carcinoma in the proximal esophagus. The following day another plastic tube was placed in the proximal esophagus successfully, but x-ray showed that the proximal end of the plastic tube was inferior to the proximal margin of the neoplasm. Some overhanging carcinoma was then removed and

*Unpublished data of Dr. Arnold M. Seligman and associates.

the plastic tube was adjusted without difficulty. On the first postoperative day the patient had difficulty in swallowing but this gradually cleared and continued to do so. On the fourteenth postoperative day the patient was started on a brief course of treatment with a new alkylating agent* which resulted in a temporary leukopenia. The patient had been losing weight gradually, refused to eat, and began to show signs of some difficulty in swallowing in the following weeks. He was given parenteral feedings with the view to adjustment of the tube should he show signs of improvement. The patient left the hospital on March 1, 1956, and went to a nursing home. He became progressively weaker and expired the following day. Postmortem examination was not performed. He survived 3 months and 4 days following the insertion of the plastic tube.



A. *B.*

Fig. 10.—Case 4. *A*, Esophagram showing carcinoma of esophagus. *B*, Esophagram showing prosthesis in position.

DISCUSSION

The tube was designed as an alternative to gastrostomy and jejunostomy and as a partial solution to family and hospital problems in feeding these starving patients.

Most of these cancers are not curable by surgery and many of these elderly patients are too debilitated to withstand major surgery. Although x-ray treatment will palliate some of these patients, their obstructing lesions may not be opened promptly by such treatment but are apt to become even more obstructed from edema. This makes treating these starved and dehydrated patients even more difficult and, doing so on an ambulatory basis, often impossible. The plastic prosthesis makes likely the restoration of nutritional and fluid balance promptly before and during x-ray therapy. The plastic tube does not obstruct the x-ray and thus does not interfere with therapy.

*Unpublished data of Dr. Arnold M. Seligman and associates.

The nylon tube is quite reactionless and light in weight. This may be why it resides in the carcinoma without producing pressure necrosis or abscesses for long periods of time. A complete understanding of the usefulness and limitations of this prosthesis must await further experience with it.

SUMMARY

1. A plastic tube has been designed on the screw principle for palliating patients with obstructing, inoperable carcinoma of the esophagus.

2. The tube is inserted through an esophagoscope with the aid of topical or inhalation anesthesia.

3. The tube obviates the necessity of gastrostomy or jejunostomy.

4. It is useful in alimentation of patients with carcinoma of the esophagus during x-ray therapy.

5. Insertion of the tube does not require previous dilation.

6. It is screwed or reamed through the growth along a bougie and thus provides for snug fit for long periods of time.

7. It permits prompt feeding after the effects of anesthesia have worn off and allows early institution of x-ray treatment.

8. If there is overgrowth of the tumor causing obstruction at a later date, the tube can be adjusted through an esophagoscope in an upward or downward direction. If it is overgrown at both ends or if it fits loosely, it can be replaced by a suitably sized tube. The patient should be checked by esophagram every 6 or 8 weeks for position of the tube.

9. The results in 4 cases are described.

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THE MASSIVELY BLEEDING DUODENAL ULCER WITH ESPECIAL REFERENCE TO CRATER

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THE subject of gastrointestinal hemorrhage, especially from the upper gastrointestinal tract, has been difficult to analyze because of variable statistics from different centers. Inherent bias exists in some of these statistics due to several factors, among which are the method of case selection and the failure of adequate definition. Statistics which include all upper gastrointestinal bleeders will combine groups of varied etiology (sometimes unknown) and, therefore, of varied prognosis. Mortality figures and conclusions based on this type of series, if not adequately broken down, are meaningless in terms of individual disease entities and are of even less value in terms of individual patients. Where peptic ulcer patients alone are considered, the figures for duodenal and gastric ulcers must be carefully separated. It has been shown frequently in the past that there may be a large difference in mortality depending on the location of the ulcer.[2, 5, 7, 15] In these days when early diagnosis can be made, there is no reason why these groups of patients should not be considered separately.

This study was undertaken with the view of analyzing one segment of all upper gastrointestinal tract bleeders admitted to a large general hospital. The figures that we obtained apply to massively bleeding duodenal ulcer patients only. The charts were reviewed retrospectively with the intention of accumulating data and follow-ups of some significance to the management of this type of patient. Special attention was paid to radiographic reports in order to correlate these with the subsequent course of the patient both inside and outside of the hospital.

The battle between internist and surgeon over the management of these patients has been resolved in most centers with an air of cooperation between the two groups. How much difference of opinion still exists is difficult to glean from published reports. It is certain that there are some patients who could have been saved by earlier surgery and others in whom surgery might best have been avoided. We must often rely on the experiences of those who have collected and published large series of these patients to determine the proper choice of treatment. We must not allow our clinical impressions to guide us, for these may frequently become clouded by our own prejudice. It is important, therefore, that the figures with which we become involved be both reliable and valid. Both internist and surgeon must be informed on

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the most modern concepts in the treatment of these patients. They must be equally discerning in their interpretations of published data; and such must be assumed in large centers.

The internist alone usually has the responsibility of evaluating the importance of concomitant diseases which are often present in these patients. The surgeon alone has the responsibility of improving his surgical technique and care so that the maximal survival may be obtained. Together they must start the patients on the road to recovery with minimal loss of life.

Admissions to The Mount Sinai Hospital are almost invariably on an ambulatory basis. Occasionally a private ambulance is employed to conduct a patient to the hospital for admission. There is no ambulance service associated with the hospital.

The patient who has time to go to his private physician with a complaint of tarry stools and is referred in for admission is far different from the patient who faints after a massive hematemesis and is brought to the hospital by ambulance. The importance of this difference has been stressed by Hinton.[13] Most of our patients fit into the former group, although the latter is also well represented.

DEFINITION OF TERMS

In order to fit into the category of massive bleeding, a patient had to have had a recent episode of melena or hematemesis (one week) and a hemoglobin during the course of hospitalization of 8 Gm. per cent or less. Two patients who had a massive hematemesis, a sudden 3 Gm. drop in hemoglobin, and fall in blood pressure were included, although recorded hemoglobin values lay between 8 and 8.5 Gm. per cent. One of these patients was rushed to the operating room almost immediately subsequent to this episode.

All of these patients bled from duodenal ulcers as far as could be determined. All were proved to have duodenal ulcers by x-ray, autopsy report, or at surgery. No patient who had another lesion which could have accounted for the bleeding was included. Excluded from the series were one patient with thrombocytopenia purpura, one with a leiomyoma of the stomach, and several patients who were found to have esophageal varices, gastric ulcer, or gastric carcinoma along with their duodenal ulcers. This left us with a group of massive upper gastrointestinal bleeders with duodenal ulcer as the sole cause for the bleeding. These patients were divided into 5 groups for the basis of analysis, depending on the amount of blood utilized for stabilization during the admission: Group I, 0 to 1 unit of blood (500 c.c. each); Group II, 2 to 4 units of blood; Group III, 5 to 6 units of blood; Group IV, over 6 units of blood; and Group V, a special group comprised of the most severe bleeders who either exsanguinated from their disease or who were rushed to surgery for fear of exsanguination. By definition all of the medically treated mortalities occurred in this last group (none of which utilized less than 8 units of blood). It is realized that the patients in Groups I and II would not be considered massive bleeders by some observers[5, 6] because of the ease with which they stabilized, and this will be considered later in calculating the mortality.

MATERIAL STUDIED

The series under investigation extended from 1947 to 1957 (Table I). There were 1,087 patients admitted with a diagnosis of duodenal ulcer, 352 patients were admitted with a diagnosis of gastric ulcer, and 200 patients were admitted with a diagnosis of upper gastrointestinal bleeding of unknown etiology. Another 35 patients had both gastric and duodenal ulcers. Of the 352 gastric ulcer patients, 51 were admitted because of massive bleeding. These patients were not considered in this paper. Of the 1,087 duodenal ulcer patients, 235 were admitted for massive bleeding or bled massively after admission (accounting for 261 admissions). One hundred and sixty-one additional duodenal ulcer patients had bleeding as their major complaint, but not severe enough to allow them to be included in this report. This is an incidence of bleeding in duodenal ulcer admissions of 36.4 per cent (396 of 1,087 patients) and an incidence of massive bleeding (as defined) in duodenal ulcer admissions of 21.6 per cent.

TABLE I. PEPTIC ULCER PATIENTS ADMITTED TO WARD SERVICE
(The Mount Sinai Hospital, January, 1947, to May, 1957)

Total duodenal ulcers	1,087
Massively bleeding duodenal ulcers	235 (21.6%)
Total gastric ulcers	352
Massively bleeding gastric ulcers	51
Gastric and duodenal ulcers	35

The Mount Sinai Hospital has, to date, been oriented toward the medical aspects of cure for these patients. This accounts for the fact that 204 of the 235 patients were admitted to the medical services (224 of 261 admissions). Surgery, when performed, was rarely done during the first 72 hours of admission. When it was performed during the bleeding admission, it was done so, usually after all evidences of bleeding had disappeared. Some of the patients who had surgery performed on readmission were actively bleeding.

AGE AND SEX

The age and sex distribution in this series is noted in the accompanying charts (Tables II and III). The distribution was seen to be similar to that reported in other series.[17, 24] One hundred and seventy-four patients were over 40 years of age. This represents the group of patients that can withstand prolonged anemia or tissue anoxia the least and, therefore, will account for the major portion of the mortality figures.[16, 17] The distribution according to age was similar among the different bleeding groups and suggests that the older patient is not more likely to bleed massively than to have a less severe bleeding episode.

The preponderance of this diathesis in men can be noted from the charts. Over-all, the ratio of men to women was a little over 2 to 1. It ranged from 1.5 to 1 and 2 to 1 in Groups I and II, respectively, to roughly 3.5 to 1 in Groups III, IV, and V.

TABLE II. SHOWING AGE DISTRIBUTION OF PATIENTS PER BLEEDING GROUP

GROUP	1 TO 20 YEARS	21 TO 39 YEARS	40 TO 59 YEARS	60 YEARS OR OVER
I	0	10	13	6
II	4	27	51	42
III	1	11	13	14
IV	0	4	15	6
V	1	3	5	9
Total	6	55	97	77

TABLE III. SHOWING SEX DISTRIBUTION OF PATIENTS PER BLEEDING GROUP

GROUP	MALES	FEMALES
I	17	12
II	80	44
III	31	8
IV	20	5
V	13	5
Total	161	74

The better prognosis of this disease in women has been noted frequently before[14, 15] and, while of interest, has not been adequately explained and is difficult to apply in the individual case.

SYMPTOMS

Melena was, by far, the most common symptom, followed by hematemesis, signs of weakness, vertigo or fainting, and epigastric pain. Hematemesis occurred in 19 per cent of Group I patients and 28, 42, 35, and 50 per cent of Groups II, III, IV, and V, respectively. Melena was remarkably constant, occurring in about 85 per cent of patients in each group. Pain was present in about 19 per cent of each group with little change in incidence among the groups. Signs of weakness or fainting occurred in roughly 40 per cent of patients in each group. In the less severe bleeders this was manifested as mild weakness or lightheadedness, and in the more severe bleeders syncope or collapse was prominent. As mentioned elsewhere, hematemesis and collapse remain the most important symptoms which may indicate the severity of the particular bleeding episode.[2, 5, 15]

An analysis of the duration of previous symptoms and number of previous bleeding episodes with relation to severity of bleeding was made. No attempt to divide these ulcers into acute and chronic was made, as has been done in the past, especially in the British literature.[15, 16] The data are summarized in Tables IV and V. Of significance, is the fact that, in 53 of the 235

TABLE IV. DURATION OF PREVIOUS ULCER SYMPTOMATOLOGY IN RELATION TO BLEEDING GROUPS

GROUP	NONE	LESS THAN 1 YEAR	1 TO 4 YEARS	5 TO 9 YEARS	10 OR MORE YEARS
I	5	3	9	4	10
II	24	8	38	32	38
III	11	3	9	5	15
IV	7	0	8	5	9
V	6	1	4	2	5
Total	53	15	68	48	77

TABLE V. NUMBER OF PREVIOUS BLEEDING EPISODES IN RELATION TO BLEEDING GROUPS

GROUP	NONE	1	2	3	OVER 3
I	15	12	1	2	1
II	75	35	16	7	7
III	27	9	3	1	3
IV	14	8	5	1	1
V	13	0	4	0	1
Total	144	64	29	11	13

patients, no evidence of previous symptomatology could be elicited. Thirteen of 47 patients in Groups IV and V, had no previous symptomatology. Seventy-seven patients had symptoms of ulcer for over 10 years.

For the majority of patients, this was the first bleeding episode of any kind (144 patients). Twenty-seven of 47 patients in Groups IV and V fell into this category.

TREATMENT

Purely medical treatment was offered to 188 of the original 235 patients. Forty-seven patients underwent surgery during the original admission and an additional 47 patients underwent surgery at the time of readmission. The indication for surgery was bleeding (either multiple episodes, recurrent, or uncontrollable massive) in almost every instance.

MORTALITY AND MORBID ANATOMY

Of the 188 patients treated by purely medical means, 7 patients died, a mortality percentage of 3.7 per cent. These patients had transfusions 8 to 33 times. All 7 patients were over 56 years of age; there were 6 men and one woman.

Of the 47 patients undergoing surgery at the first admission, 3 died, a mortality percentage of 6.4 per cent. Of these 3 patients, one was a child of 6 years who was subjected to an exploratory laparotomy for bleeding which was unsuccessful in locating the lesion. He continued to bleed postoperatively and expired. At postmortem examination, an acute ulcer of the duodenum was found which was eroding the superior pancreaticoduodenal artery.

Another patient was a 54-year-old woman, who had an emergency subtotal gastric resection performed with the base of the ulcer left in situ. She continued to bleed postoperatively and expired. No postmortem examination was obtained.

The third surgical fatality was a 57-year-old man who had a Billroth I subtotal resection plus vagotomy performed because of continuous slow bleeding with constant melena during 27 days of hospitalization on the medical service. He suffered a cardiac arrest on the operating table from which he recovered, only to die on the seventeenth postoperative day with evidence of cerebral anoxia. His hemoglobin hovered around 8 Gm. per cent during his first 25 days in the hospital, and it was not until the day prior to operation that 2 units of blood were administered. Possible errors in judgment are obvious in all of these deaths.

Pathologic findings are available in 5 of the 7 medical deaths and all of the surgical fatalities. In all of these specimens the ulcer was located on the posterior duodenal wall penetrating into the pancreas. Erosion of the superior pancreaticoduodenal artery or one of its branches was present in 5. Of the 18 patients in Group V, pathologic details are available in 14. In all of these the ulcer was located on the posterior duodenal wall.

Of the 47 patients who underwent surgery at the time of readmission, an additional 3 patients died. The over-all surgical mortality with bleeding as an indication (but not necessarily all massive bleeding) was, therefore, 6.4 per cent. Information was obtained to see which of these patients were bleeding actively at the time of surgery, as evidenced by melena, hematemesis, or a falling hemoglobin. Twenty-four of the 94 patients operated on fell into this category, and 5 of the 6 deaths occurred among these patients (20.8 per cent). Of the truly elective procedures (bleeding subsided), there was one death in 70 patients (1.4 per cent) (Table VI). Of these 5 deaths in the actively bleeding surgically treated patients, 4 patients were operated upon 4 to 33 days after admission (one patient used 34 units of blood preoperatively). The remaining patient was the woman mentioned earlier who had the base of the ulcer left in at the time of surgery. It is interesting to note that 2 of the 5 deaths occurring in the actively bleeding group had a vagotomy and gastroenterostomy as the primary procedure. We do not, at this time, subscribe to this operation alone in the treatment of active bleeding. It is our belief that if it does have a place in the treatment of bleeding ulcer, it must be accompanied by ligation of the bleeding point in the ulcer. The over-all mortality of both medically and surgically treated patients was 4.3 per cent in our series.

TABLE VI. BREAKDOWN OF SURGICAL MORTALITY

OPERATION	NUMBER OF PATIENTS	MORTALITY
A. Patients undergoing surgery while actively bleeding		
Billroth II	14	1
Billroth II and vagotomy	3	0
Gastroenterostomy	0	0
Gastroenterostomy and vagotomy	4	2
Billroth I	2	1
Exploratory laparotomy	1	1
Total	24	5 (20.8%)
B. Patients undergoing elective surgery (bleeding subsided)		
Billroth II	28	0
Billroth II and vagotomy	29	1
Gastroenterostomy	2	0
Gastroenterostomy and vagotomy	11	0
Total	70	1 (1.4%)

According to some, the differentiation of massive from nonmassive bleeders should be based upon the amount of blood utilized by the patient, with 2,000 c.c. given as the dividing line[27] and those using more than this amount being defined as massive bleeders. We agree that our Groups I and

II are highly favorable cases for any type of treatment since these patients stabilize quickly or cease to bleed soon after admission. In order not to weight our mortality figures with this type of bleeder, we recalculated them on the basis of the last 3 groups alone (over 4 units of blood). This is of significance because, with each unit of blood transfused, new probabilities arise as to the survival of the patient. One must keep constantly in mind the changing percentages in favor of and against the patient as his course in the hospital progresses.

Of 82 patients in Groups III, IV, and V, 9 died. This is an over-all mortality of 11 per cent. Of 24 patients in the above groups receiving surgical treatment during their original admission, 2 died (8.3 per cent). Of 58 purely medically treated patients in the above groups, 7 died (12.1 per cent).

FOLLOW-UP INVESTIGATION

Twenty-four of the patients in our series were readmitted with massive upper gastrointestinal tract bleeding, accounting for 26 readmissions. All of these patients had received purely medical treatment originally. This represents an absolute minimal failure rate of medical treatment of 12.8 per cent in our hands. These are patients whose lives were in jeopardy twice from their disease.

Follow-up data are summarized in Tables VII, VIII, and IX. Of 188 patients treated medically in our series, 104 were followed for a period of over

TABLE VII. SUMMARY OF MEDICALLY TREATED PATIENTS

Number of patients treated medically	188 (80%)
Mortality	7 (3.7%)
Number of patients followed over one year	104 (57.5%)
Average length of follow-up	5.1 years
Bled again after discharge	53 (50.9%)
Came to subsequent surgery	40 (38.5%)

TABLE VIII. SUMMARY OF SURGICALLY TREATED PATIENTS

Number of patients treated surgically	47 (20%)
Mortality	3 (6.4%)
Number of patients followed over one year	28 (63.6%)
Average length of follow-up	4.7 years
Bled again after surgery	3 (10.7%)

TABLE IX. SUMMARY OF SURGICALLY TREATED PATIENTS PER OPERATION TYPE (INCLUDING THOSE MEDICALLY TREATED ORIGINALLY AND REQUIRING SUBSEQUENT SURGERY)

OPERATION	NUMBER OF PATIENTS	MORTALITY	NUMBER FOLLOWED OVER 1 YEAR	NUMBER WHO BLED AFTER SURGERY
Billroth II	42	1 (2.4%)	25 (60.9%)	5 (20%)
Billroth II and vagotomy	32	1 (3.1%)	25 (78.1%)	2 (8%)
Gastroenterostomy	2	0	2 (100%)	1 (50%)
Gastroenterostomy and vagotomy	15	2 (13.3%)	7 (53.8%)	3 (43%)
Billroth I	2	1 (50%)	0	-
Exploratory laparotomy	1	1 (100%)	0	-
Total	94	6 (6.4%)	59 (67.0%)	11 (18.6%)

one year (average 5.1 years). This is a 57.5 per cent follow-up excluding the 7 who died during admission. Of these 104 patients, 53 bled again after discharge (50.9 per cent), and 40 (38.5 per cent) came to elective surgery or were operated on during a period of recurrent bleeding. Patients who were operated upon or who bled but whose total follow-up came to less than a year are excluded from these calculations.

Of the original 47 surgically treated patients, 28 (63.6 per cent) were followed over one year (average 4.7 years) and 3 (10.7 per cent) had recurrent bleeding after discharge. In order to more fully evaluate surgical therapy for this disease, we included in follow-up an additional 31 patients who had subsequent surgery (part of the group originally treated medically). This brings our follow-up to 59 of 94 patients (67 per cent) treated surgically for bleeding duodenal ulcer, and 11 of these patients bled again (18.6 per cent).

A breakdown of mortality and recurrent bleeding after different surgical procedures is given in Table IX. Although the numbers may be small, certain observations are available. The addition of a vagotomy to a Billroth II subtotal resection decreased the incidence of recurrent bleeding from 20 to 8 per cent. Another observation is the futility of performing a gastroenterostomy, with or without vagotomy, or Billroth I subtotal resection for these patients. Three of our 6 surgical deaths occurred in these groups although they only represented 19 of 94 operations; and 4 of 11 patients who bled subsequently did so after these procedures.

TABLE X. DISTRIBUTION OF CRATERS IN ROENTGENOGRAMS AMONG BLEEDING GROUPS

GROUP	WITH CRATERS	WITHOUT CRATERS	INCIDENCE
I	8	20	28.6%
II	35	86	28.9%
III	17	23	42.5%
IV	13	6	68.4%
V	3	0	100%

RADIOLOGIC FINDINGS

A special aspect of this problem was devoted to the roentgenographic findings in these patients during their admission. At this hospital, x-ray examination of the gastrointestinal tract has rarely been performed in the past during the stage of active bleeding. Except for the 3 patients in Group V who had their x-rays taken before massive bleeding became manifest, the examinations were carried out when the patients were stable and usually having guaiac-negative stools. The findings were divided into two groups: those with craters and those without.

SIGNIFICANCE OF CRATER

To the radiologist, the crater is defined as the persistent presence of a localized, rounded collection of barium.[20] According to Berg, the deep crater and rolled-up margin of a callous ulcer are easy to demonstrate, but in ulcers confined to the superficial mucosa the crater may be so shallow that it is quite

impossible to demonstrate it roentgenologically in the living subject.[4] The presence of a crater on x-ray indicates that the ulcer has penetrated into submucosa or muscle.[25]

In our series, remarks as to the presence of a persistent patch or fleck of barium in the bulb were considered as evidence of crater. If only radiation of folds was mentioned, it was considered part of the no-crater (deformity only) group. The facts that came to light during this investigation are summarized in Tables X and XI.

TABLE XI. COMPARISON OF ROENTGENOLOGIC FINDINGS IN PATIENTS TREATED MEDICALLY (WHO HAD X-RAYS) AND FOLLOWED AT LEAST ONE YEAR OR UNTIL RECURRENT BLEEDING OR SURGERY

FINDINGS	NUMBER OF PATIENTS TREATED MEDICALLY	NUMBER OF PATIENTS FOLLOWED	NUMBER OF PATIENTS WITH RECURRENT BLEEDING	NUMBER OF PATIENTS UNDERGOING SURGERY
Crater	65	40	29 (72.5%)	24 (60%)
No crater	119	75	30 (40%)	20 (26.7%)
Total	184	115 (62.5%)	59 (51.3%)	44 (38.3%)

Crater was a more constant finding in the more severe bleeding groups, being present in 28.6, 28.9, 42.5, 68.4, and 100 per cent of patients who had x-rays in Groups I to V, respectively. It was also noticed that there was a difference in the prognosis with respect to recurrent bleeding and subsequent surgery among medically treated patients depending on whether or not craters were demonstrated during hospitalization for bleeding. Of those medically treated and not demonstrating craters (119 patients), 40 per cent bled again and 26.7 per cent required subsequent surgery of those followed. Of those medically treated and demonstrating craters (65 patients), 72.5 per cent bled again and 60 per cent required subsequent surgery of those followed (difference significant $p = 0.001$).

DISCUSSION

A group of 100 massive bleeders reported from one institution may bear little resemblance to a group of 100 massive bleeders from another. We should be aware of the number of different types of bleeders in each series, for the mortality will vary in each type. We should be aware of the selection of patients that is inherently involved with the different sources of patient material in various centers. The definition of the term "massive bleeder," used by the authors, as well as the methods by which the diagnosis is confirmed, is of great importance to the proper analysis of the statistics. Hemoglobin levels are sufficient only if the subsequent course of the patient is taken into consideration. For example, Finsterer showed that if hemoglobin levels were dropped to 40 per cent or below and red blood cell count to 2.5 million or below, the mortality could be made to increase from 2 to 5 per cent to 11 to 25 per cent. In our series, the difference in definition of the term massive bleeder accounted for a change in mortality of medically treated patients from 3.7 to 12.1 per cent.

In the bleeding duodenal ulcer group taken as a whole, medical treatment is the most favorable method of immediate treatment. We should distinguish, after 24 to 48 hours of medical therapy, a separate group of these patients still

necessitating transfusion after having received 2,000 c.c. of blood. The mortality of this latter group will be better with early surgical treatment than with medical. Exception may be made in those patients under 45 years of age, where an additional 24 hours' observation may be allowed. Needless to say, patients who utilize this 2,000 c.c. of blood in under 24 hours should be candidates for immediate surgery. If after 48 hours the patient is still bleeding as evidenced by fresh blood via the Levine tube, unmaintained hemoglobin, or recurrent hematemesis, then the patient should be taken directly to the operating theater. Should he recover on medical treatment, he has a 50 per cent chance of bleeding again and a 12 per cent chance of bleeding again massively (our figures). On the other hand, should surgery become necessary after this critical period in active bleeding or during active bleeding on a subsequent admission, then the mortality becomes very high.

The figures quoted in other series are not dissimilar from the ones found by us. Heuer[12] reported a 29 per cent mortality in patients undergoing surgery while actively bleeding as opposed to 4 per cent in those undergoing elective surgery. He mentions a 10 per cent mortality in those undergoing early surgery as opposed to 70 per cent in those undergoing late surgery. Fraser and West[10] found a 33.3 per cent mortality in late surgery for actively bleeding duodenal ulcer. The figures often quoted from Finsterer[9] are 33.3 per cent for late operation as against 5.1 per cent for early operative intervention.

Previous attempts to compare surgical and medical mortalities have been grossly biased by the failure to realize that the surgical figures used were those of late surgery. Operations on patients under these conditions were done after a trial of medical therapy had failed. For a proper comparison only figures of early surgery should be compared with medical treatment at the same institution. This would also tend to control such variables as selection of cases and definition of terms. Stewart[23] reported on 65 patients with surgically treated massively bleeding peptic (includes gastric) ulcer, only 5 of whom were operated on late, with a 10.7 per cent mortality. This is opposed to 42 medically treated patients with a 21.4 per cent mortality. Our mortality figures are lower because we excluded all gastric ulcers. Jones[16] has stated that where he formerly treated all these patients almost solely by medical means, he now maintains a sharp surgical bias with respect to emergency surgery. Concomitant disease in the older age groups is an indication for earlier surgery, not a contraindication. These patients cannot tolerate the effects of tissue anoxia due to prolonged anemia.[2, 19, 23]

If the immediate salvage of the patient is the only consideration in his treatment then follow-up statistics have nothing more than academic interest. It is true that the majority of patients who bleed massively do not bleed massively again,[14] although the occurrence of minor bleeding episodes is frequent.[6, 22] However, how can one consider a particular plan of management successful just because the patient leaves the hospital alive, if he is to return once again prey to the ravages of his disease. In addition, who can estimate the price of recurrent melena with concomitant anemia that must be paid by the tissues of the body. Statistics to evaluate this factor are not as yet available.

The burden of improving the prognosis in these patients lies heavily on the shoulders of the surgeon. Hasty surgery is not the answer. Treatment of the bleeding point alone is not the answer. One must keep in mind the significance of the "ulcer diathesis" in these patients. Subtotal gastric resection is the best method of surgically dealing with this problem that we have at hand at this time. Ligation of the involved vessel should be accomplished wherever possible. Recurrent bleeding after surgical treatment in our series agrees with that found by Boles' group,[6] although our figures for medically treated patients disagree. Other series report the incidence of recurrent bleeding after medical treatment as high as 70 per cent.[5] The fact that a large difference in recurrent bleeding was present between those patients who had a Billroth II and those who had a Billroth II plus vagotomy (20 vs. 8 per cent) leads us to assume that the addition of a vagotomy at the time of original surgery may prove a valuable adjunct to the surgical treatment of these patients.

The large number of previously asymptomatic patients in our series is one of the most cogent arguments in favor of early x-ray examination. Certain observations are common in treating these patients. They rarely bleed steadily to exsanguination. The course of the bleeding usually has peaks and valleys during which the patient may appear to stabilize before being subjected to another massive hematemesis. Opportunities for these early examinations are present. Careful studies of pathologic material, reported elsewhere, have demonstrated the reason for these observations. Thrombi have been demonstrated in the eroded vessels at the base of bleeding ulcers.[2, 7, 18, 19] The significance of this is that these people do maintain their hemostatic mechanisms. It is the re-erosion of these thrombosed vessels that produces the intermittent bleeding. In our present state of knowledge, we must assume that it is the acid peptic factor that is involved and it is with this that we must deal.

Incidentally, there is little evidence to support the contention that arteriosclerosis occurs in older patients in the involved vessels, preventing retraction. Studied material indicates that necrosis of the arterial wall occurs during acute erosion, breaking up the elastic fibrils and thus preventing retraction.[18] The increased mortality of this disease in the older age groups need not be explained on the basis of local vascular factors but can be explained on the basis of more generalized bodily changes.

The posterior wall ulcer is not the only one that bleeds. Duodenal ulcers in other locations may bleed enough for the patient to be classified as a massive bleeder. However, the ulcer in which bleeding becomes a hazard to the life of the patient will almost always be located on the posterior duodenal wall,[2] usually penetrating into the pancreas, and often eroding a large artery.[12] The significance of persistent pain as a bad prognostic sign, as noted frequently by Jones,[15, 16] we believe is related to this phenomenon. Anything which will give us a clue to the location of such an ulcer early in its course would be of great value in the management of the patient.

As mentioned earlier, the emergency roentgenologic examination is of value in establishing or confirming the diagnosis. If the patient is not in

severe shock or actively vomiting, this can be done safely and effectively.[1, 11, 21, 27] We know that duodenal ulcer can be diagnosed on x-rays taken during active bleeding.[8, 21] We know that craters can be demonstrated without palpation or compression.[8, 11] There is no good evidence in favor of increasing the chance of recurrent bleeding. We have recently gone so far as to empty a stomach filled with clotted blood, by means of an Ewald tube in order to get confirmation of the lesion by roentgenologic techniques.

The presence of an ulcer crater on x-ray does not preclude its presence on the posterior wall and in that sense make it more likely to bleed massively. However, we have found a significant difference in prognosis in our series depending on whether or not a crater was demonstrated on x-ray. The presence of a late crater is evidence that the patient has had a protracted course as seen by the increasing frequency of their appearance in the more severely bleeding patient. We cannot draw any conclusions as to the value of craters appearing early in the course of a bleeding episode or on a previous admission from our present data. The size and location of the ulcer crater may also be important. These aspects of the problems still need to be investigated.

Craters have been known to disappear on medical therapy for duodenal ulcer,[8] including those that have been bleeding. However, the presence of a crater late in the course of a medically treated bleeding duodenal ulcer patient, we feel, indicates some intractability of the disease and would tend to make us lean toward surgical therapy for this ulcer before the patient is discharged. Almost 3 out of 4 of these patients will bleed again and over half will come to subsequent surgery in any case!

It is, therefore, suggested that a patient demonstrating a crater on emergency gastrointestinal series during bleeding will have a longer and more protracted course and poorer prognosis for cure than one demonstrating only a deformity of the bulb. If this proves to be a valid assumption, then another tool is at hand to aid us in the management of these patients.

SUMMARY AND CONCLUSIONS

1. An analysis was undertaken of 235 patients with massively bleeding duodenal ulcers admitted to the wards of The Mount Sinai Hospital from 1947 to 1957.

2. The patients were divided into four bleeding groups on the basis of the number of units of blood they utilized in order to stabilize. The fifth group was made up of patients who exsanguinated on medical therapy or who were rushed to the operating room for emergency surgery.

3. The mortality among 188 medically treated patients was 3.7 per cent. The mortality among 47 surgically treated patients was 6.4 per cent.

4. The mortality of an additional 47 surgically treated patients who bled after discharge or were done electively was 6.4 per cent.

5. The surgical mortality during active bleeding was 20.8 per cent as opposed to 1.4 per cent for purely elective procedures.

6. The medical mortality in the last 3 groups (over 2,000 c.c. of blood) was 12.1 per cent. The surgical mortality in these same patients was 8.3 per cent.

7. Follow-ups of 104 medically treated patients revealed a 50.9 per cent incidence of recurrent bleeding as opposed to 18.6 per cent of all surgically treated patients.

8. Billroth II subtotal gastric resection plus vagotomy yielded the lowest incidence of recurrent bleeding (8 per cent).

9. Review of roentgenographic findings in these patients revealed a higher incidence of crater in the more severe bleeding groups.

10. Follow-up of patients treated medically revealed that when no crater was demonstrated during the hospitalization for the bleeding episode, the incidence of recurrent bleeding was 40 per cent. When a crater was demonstrated during hospitalization, bleeding recurred in 72.5 per cent of the patients.

11. Follow-ups on medically treated patients revealed an incidence of subsequent surgery of 26.7 per cent if no crater was demonstrated and 60 per cent if a crater was demonstrated.

12. It is suggested that patients with acute massive hemorrhage of duodenal ulcer origin be operated upon much sooner when a crater is demonstrated roentgenologically.

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SPONTANEOUS BILIOBRONCHIAL FISTULA FORMATION FOLLOWING COMMON DUCT OBSTRUCTION

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COUGH and the production of large amounts of sputum are not always due to primary intrathoracic disease. An uncommon cause for this picture is a subphrenic abscess with a contiguous pleuritis, rupture through the diaphragm, and subsequent biliobronchial fistula formation. In 1938, a review by Ochsner and DeBakey[5] of 1,380 cases of subphrenic abscess showed that a simple pleuritis occurred in 28 per cent, perforation and empyema in 18 per cent, and biliobronchial fistula formation in 10.5 per cent. In 12.6 per cent of their cases the primary pathology was in the liver and biliary duct system.

Etiologically the cases of biliobronchial fistula can be divided into three groups: (1) traumatic, (2) those due to amebic and echinococcus disease in the liver, and (3) cholelithiasis with secondary suppuration within the biliary duct system. Our case falls into this third group.

In 1890 Courvoisier collected 24 cases of hepatopleural and biliobronchial fistulas, the exact number of which were biliobronchial is not stated. In 1897 Graham[2] added two cases to the literature. In 1928 Morton and Phillips[4] reported a case and made a comprehensive review of the literature, collecting 50 cases of biliobronchial fistulas exclusive of those due to amebic and echinococcus disease of the liver.

The diagnosis is usually apparent. The patient has a past history suggestive of biliary duct disease. The presenting picture is that of a right lower lobe pneumonia and bronchiectasis productive of large amounts of green sputum. The laboratory can quickly confirm the presence of bile in the sputum.

The pathogenesis is centered around the obstruction of any of the biliary ducts and the resultant secondary infection which leads to a communication with the subphrenic space. This leads to a contiguous pleuritis, rupture through the diaphragm, and the formation of a biliobronchial fistula.

Treatment should be directed at the cause of the fistula and not at the fistula itself, which means relief of the biliary duct obstruction. The biliobronchial fistula will then close spontaneously. The fistula tract should not be approached through the diaphragm for two reasons: (1) the tracts are very small and devious in their paths,[1] and (2) even if the tract were removed thoracically and the biliary duct obstruction were permitted to persist the fistula would certainly recur.

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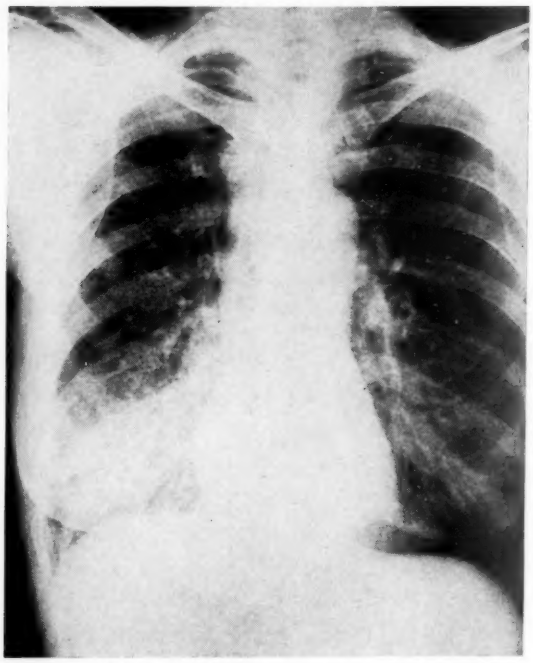
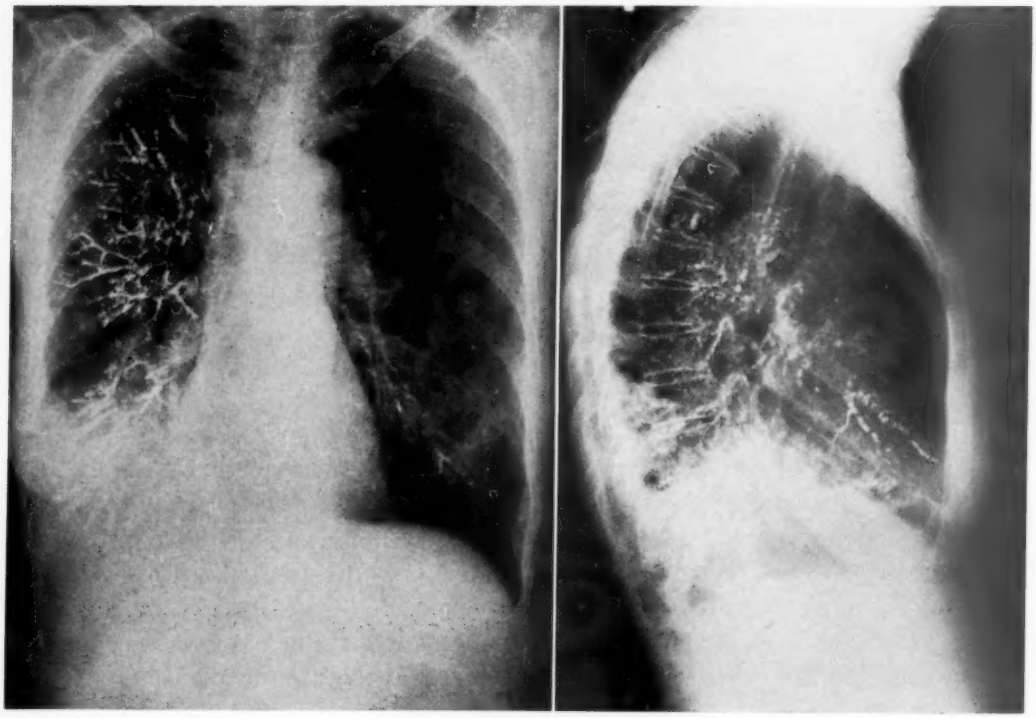


Fig. 1.—Posteroanterior chest film taken on the last hospital admission following a 3-week cough productive of bile-stained sputum.



A. *B.*

Fig. 2.—Posteroanterior (*A*) and lateral (*B*) films of a right bronchogram made following a 3-week cough productive of bile-stained sputum.

CASE REPORT

A 40-year-old white woman had right-sided abdominal pain. A normal gall bladder and appendix were observed at surgery and an appendectomy was performed. At the age of 57 she complained of right upper quadrant abdominal pain. At surgery 6 stones were removed from the gall bladder and a cholecystostomy was performed. The wound drained for 14 months. She again complained of right upper quadrant pain at the age of 67. Gangrene of the gall bladder was found and a cholecystostomy was performed. Six months later she was first seen at the Presbyterian Hospital by Dr. Vernon C. David. She presented the picture of intermittent common duct obstruction. At surgery a common duct stone was found. The stone was removed, the common duct was decompressed by a T tube, and a cholecystectomy was performed.

Two years later she developed a right upper quadrant abscess. This was drained. Two years later at the age of 71 she had pneumonia of the right lower lobe. This responded to treatment, but she returned 4 months later and was seen for the first time by one of us (R. K. G.). She had a history of coughing and wheezing which was productive of large amounts of green sputum of 3 weeks' duration. The levels and movements of the diaphragms were normal. The right lower lobe presented clinical and x-ray evidence of pneumonia (Fig. 1). A severe right lower lobe bronchiectasis was seen on a bronchogram (Fig. 2), but a fistula between the bronchial tree and the liver could not be demonstrated. At surgery, cardiac arrest occurred as the skin incision was made. A thoracotomy was performed, and the heart was found in standstill. Manual compression of the heart was begun, and 5 minutes later the heart resumed a regular rhythm. The chest was closed without further surgery. Following this she continued to cough up large amounts of sputum containing bile. She was slowly but progressively becoming worse. One month later she was again taken to surgery. Under topical 5 per cent cocaine anesthesia the intratracheal tube was inserted. Then with local 0.5 per cent procaine anesthesia supplemented by a light general anesthetic, the abdomen was opened. Dense adhesions filled the upper abdomen. Both lobes of the liver, the duodenum, and the right colon were mobilized. The diaphragmatic attachments of the liver were freed until only the vascular bundle remained undisturbed. A fistula could not be identified. The common duct was dilated and an olive-sized stone was impacted at the ampulla of Vater. The stone was removed and the common duct was decompressed by T tube. Postoperatively the cough and pneumonia cleared. The production of bile-stained sputum ceased. Today, 4 years later, she is symptom free at age 75 years.

CONCLUSIONS

1. Biliobronchial fistula is an uncommon complication of biliary duct obstruction.

2. The fistula can rarely be demonstrated by bronchogram, operative cholangiogram, or surgical exploration.

3. The surgical approach to the biliobronchial fistula is through the abdomen.

4. Removal of the obstruction to the common duct will result in the spontaneous closure of the fistula.

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DISRUPTION OF MUSCLES AND TENDONS

An Analysis of 1,014 Cases

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EVERY muscle-tendon unit in the body contracts innumerable times daily. Both muscles and tendons are susceptible to trauma and wear-tear stresses and strains. Despite these facts, reports of large series of cases involving loss of continuity or disruption of muscles and tendons are relatively rare in the literature. Authors disagree as to most common sites, etiology, contributing factors, and methods of treatment. It is the purpose of this paper to present a statistical analysis of 1,014 cases of disruption of muscles and tendons encountered at the Mayo Clinic. Later papers will deal with some special aspects of this problem and will discuss treatment.

HISTORICAL REVIEW

The first case of disruption of muscles and tendons was reported in 1722 by Petit,[15] who cited a case of rupture of the quadriceps mechanism. In 1882 Maydl[13] reviewed 230 cases reported in the literature. Forty years later, Grassheim,[6] reporting on 500 cases that included most of those reported to that time plus cases encountered in his own practice, said that the muscles of the calf, the extensors of the leg, and the biceps brachii were the three most common sites of rupture of muscles and tendons.

Gilcreest,[3] who was responsible for stimulating much of the original interest in ruptures of muscles and tendons in this country, felt that the Achilles tendon, quadriceps, biceps, triceps, and rectus abdominis were the most frequent sites of injury. Brickner and Milch[2] in 1928 agreed with Gilcreest as to frequency of muscle and tendon injuries. They also felt that the adductors of the thigh and the lumbar muscles were most likely to suffer partial tears.

In 1935, Haldeman and Soto-Hall[7] in an analysis of 100 cases found that tears affected muscles and tendons in the following order of frequency: supraspinatus, long head of biceps and finger extensors in the upper extremity, and the quadriceps mechanism and triceps surae in the lower extremity. In their series, there were 4 cases of rupture of the rectus abdominis. This muscle was the only trunk muscle so involved. The average age of patients with disruption was 42.5 years.

A search of the English-language literature since 1935 does not reveal any review of a large number of muscle and tendon injuries. There have been

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many reports, however, centering on disruptions in the wrist, hand, knee, and ankle.

Vaughan-Jackson,[18] in 1948, reported on 2 patients with rupture of the common extensor tendons to the fingers due to arthritic changes at the inferior radioulnar joint. In reviewing the literature for a 31-year period he was unable to find a similar example. The same year Kersley[10] cited a case associated with rheumatoid arthritis, and Gladstone[5] added 2 cases in 1950, both associated with malunion of old fractures about the wrist.

Eighty-five cases of disruption of the extensor pollicis longus associated with Colles' fracture were reported in the world literature by 1950, according to Trevor.[17] In 1955, Laine and Vainio[11] reported 3 instances of rupture of the extensor pollicis longus associated with rheumatoid arthritis and found reports of 7 similar cases in the literature. These authors reviewed 1,000 cases of rheumatoid arthritis and found, in addition to the 3 cases of disruption of the extensor pollicis longus, one rupture each of the tendon of the extensor digitorum communis and the tendon of the flexor digitorum sublimis.

Most authors have expressed the opinion that rupture of the extensor pollicis longus tendon is rare. According to Mason[12] it usually is associated with injury of the wrist, such as Colles' fracture, and according to Harris[8] it occurs approximately once per 400 such fractures.

Posch[16] said that rupture at the insertions of the extensor tendons of the fingers into the base of the distal phalanges is the most frequent type of tendon disruption, as in "baseball" or "mallet" finger.

Bate[1] found reports of 100 cases of subcutaneous rupture of the tendo achillis in the literature to 1951 and reported two cases of his own. In the late nineteenth century, Maydl[13] reported 118 tears of the extensor mechanism of the knee, but recently Hinkamp[9] could find reports of only 10 cases of bilateral rupture of the quadriceps in the English-language literature and reported a case of his own. Brickner and Milch[2] said that the patella was more apt to fracture than the tendon, and quoted Sonnenschein as saying that in 5 years of busy practice he saw 51 patients with fractured patella and only 4 patients with ruptured quadriceps. Gilcreest[4] felt that these tears occur only during active contraction of the muscle.

ETIOLOGY

Since a specific injury may be superimposed on a degenerating muscle or tendon, causative factors are not always easily ascertained. Disruptions of muscles and tendons have been attributed to many factors: senility, arthritis, rheumatoid tenosynovitis, myositis, acute infectious diseases, syphilis, tuberculosis, and tumor. Excessive fatigue, rendering muscle fibers less likely to resist a sudden pull, has been implicated. Occupational disruptions such as kettle-drummer's palsy and rider's tendon have been described. Senility is considered a major factor by most authors.

McMaster's[14] classic experiments showed that a normal tendon does not rupture under stress. Linear tension on such a tendon causes disruption at the

musculotendinous junction, in the belly of the muscle, or at the tendinous insertion. Even with 75 per cent of a tendon's fibers severed, normal activity did not cause rupture. Therefore, rupture through the substance of a tendon should occur only in diseased tissue. The cause, however, of rupture of the tendo achillis in a healthy young athlete remains unsolved, as does the unnoticed rupture of the long head of the biceps in young people. Undoubtedly microscopic damage to portions of the vascular supply to the tendon substance plays an important part in these disruptions.

Many disruptions are associated with obvious trauma. Such trauma can be in the form of a lacerating injury, a direct blow, or unusual stress placed upon the muscle-tendon unit. Unusual stress consists of subjecting a contracting muscle to severe stretching force, or a sudden and unusually forceful muscle contraction. Since many disruptions in "normal" tendons do, in fact, occur in association with trauma, one is forced to assume that minute sites of devitalization can and do occur within the tendon substance. These devitalized sites are more susceptible to disruption from increased load or direct injury.

Haldeman[7] felt that these stresses accounted for 50 per cent of the disruptions in his series; 28 per cent were due to direct trauma and 13 per cent occurred spontaneously or from unknown cause. He did not include lacerations in his study.

METHOD AND MATERIAL

Table I shows a simple classification of muscle and tendon disruptions. This type of division was found to be extremely useful in our series of cases, in which the inciting factor was usually clearly traumatic.

TABLE I. DISRUPTIONS OF MUSCLES AND TENDONS

GROUP	CLASSIFICATION
1	Lacerating injury
2	Direct injury
3	Stress rupture
4	Miscellaneous

In Group 1, the lacerating injuries, we have included all injuries that involved an open wound from any cause whatsoever. All open fractures that were associated with muscle or tendon disruptions near the site of fracture were included in this group. Group 2 includes all instances of direct injury to the site of subsequent tear without an open wound. In Group 3 are placed all disruptions associated with unusually heavy activity or situations in which a muscle or tendon was subjected to excess stress. Group 4 includes all instances of tear occurring with "normal" or everyday activity. A few case records were inadequate as to inciting factor, if any, and these unknowns were included in Group 4.

In the files of the Mayo Clinic for the period 1945 through 1954, records of 1,014 disruptions of muscles or tendons in 781 patients were found, for an incidence of approximately 70 disruptions per 100,000 patients per year. These disruptions were analyzed as to site and frequency of occurrence, etiology, relation to fractures, predisposing causes, and other details.

RESULTS

The anatomic distribution of the disruptions is seen in Table II. Disruptions of the upper extremity were six times as frequent as those in the lower extremity, and disruptions in the trunk accounted for a very small percentage of the total. The average age for the entire series of 781 patients was 40.5 years, and men outnumbered women in almost all muscle-tendon groups.

TABLE II. ANATOMIC DISTRIBUTION OF 1,014 DISRUPTIONS OF MUSCLES AND TENDONS

UPPER EXTREMITY	NUMBER	LOWER EXTREMITY	NUMBER	TRUNK	NUMBER
Flexors of fingers	216	Quadriceps mechanism	54	Left hemidiaphragm	6
Extensors of fingers	184	Tendo achillis	22	Trapezius	2
Musculotendinous cuff	182	Triceps surae	21	Rectus abdominis	2
Biceps	69	Extensors of toes	16	Intercostals	2
Extensor pollicis longus	51	Anterior tibial	10	Sternocleidomastoid	1
Flexor pollicis longus	30	Hamstrings	3	Serratus anterior	1
Multiple injuries of tendons, nerves, vessels	27	Flexor hallucis longus	3	Pectoralis minor	1
Palmaris longus	18	Posterior tibial	3		
Flexor carpi ulnaris	17	Peroneus longus	2		
Flexor carpi radialis	11	Peroneus tertius	2		
Abductor pollicis longus	10	Adductors	2		
Extensor pollicis brevis	8	Pyriformis	1		
Triceps	8	Obturator internus	1		
Thenar group	7	Sartorius	1		
Brachioradialis	5	Gracilis	1		
Extensor carpi radialis, longus and brevis	4	Adductor hallucis	1		
Extensor carpi ulnaris	4				
Hypothenar group	2				
Brachialis	2				
Interossei	1				
Total	856 (84.4%)	Total	143 (14.1%)	Total	15 (1.5%)

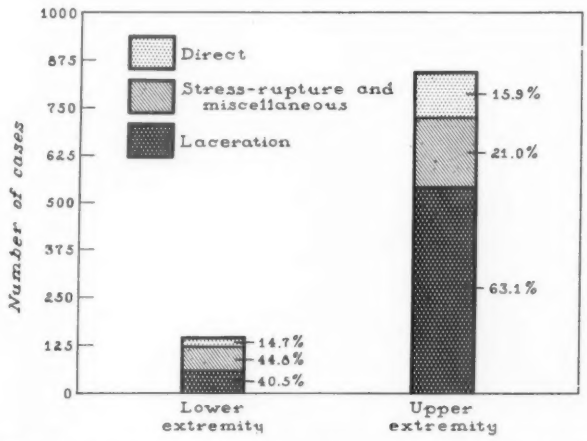

Fig. 1.—Distribution of disruptions by group and extremity.

Fig. 1 shows the relative frequency of the causes of disruption. Stress rupture and miscellaneous causes were grouped together for clarity. It is noteworthy, however, that the frequency of miscellaneous causes for disruption in the upper extremity was almost identical with that for the lower extremity, being approximately 8 per cent of the total. There were 598 disruptions due to lacerations and 416 due to other causes.

The large number of lacerations in the upper extremity is related to the frequency with which home, farm, and industrial accidents cause injuries about the wrists and hands. Direct injuries accounted for almost equal percentages of disruption in the upper and lower extremities, while stress rupture accounted for twice as many disruptions in the weight-bearing lower extremities as in the upper extremities. Disruptions were associated with fractures in 6.4 per cent of cases.

The flexors and extensors of the fingers, plus the musculotendinous cuff and biceps brachii, represented 76 per cent of the disruptions in the upper extremities. The quadriceps, tendo achillis, and triceps surae (not including the tendo achillis) represented 67.8 per cent of the disruptions in the lower extremities.

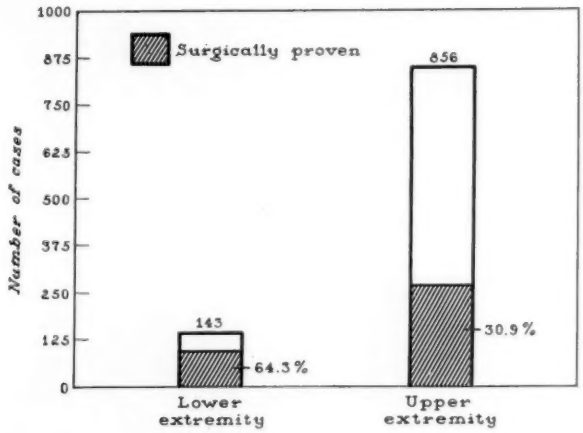

Fig. 2.—Proportion of surgically proved disruptions by extremity.

The proportion of disruptions that were surgically proved is depicted by extremities in Fig. 2. Most of the lacerations would fall automatically into this category, but many disruptions were treated conservatively and never came to operation. Again, the larger percentage of disruptions in the upper extremity that were treated nonsurgically is due to the fact that the large number of small tears of the shoulder cuff included in this group were treated by conservative methods.

Table III shows the distribution of partial disruptions by extremity and type of injury. Of 1,014 disruptions, 269 were partial or incomplete. In only

TABLE III. PARTIAL DISRUPTIONS

CLASSIFICATION	DISRUPTIONS			
	UPPER EXTREMITY		LOWER EXTREMITY	
	TOTAL, COMPLETE OR PARTIAL	PARTIAL ONLY (%)	TOTAL, COMPLETE OR PARTIAL	PARTIAL ONLY (%)
Lacerations and direct injury (Groups 1 and 2)	676	20.7	79	25.3
Stress rupture and miscellaneous (Groups 3 and 4)	180	58.8	64	31.2

one category did partial disruptions outnumber complete disruptions, and this high incidence was due to 82 partial tears of the shoulder cuff included in Groups 3 and 4.

Descriptions in Upper Extremity.—A further breakdown as to classification of injury is shown in Table IV. The flexors of the fingers were the structures most commonly disrupted in the upper extremity, and more than 94 per cent of all loss of continuity of these flexors were due to lacerating injuries. Of the disruptions of the finger extensors, 77.7 per cent were due to lacerations, as were 76.7 per cent of the disruptions of the extensor pollicis longus. These three groups of tendons were the most common sites of lacerating injuries in the upper extremity.

TABLE IV. DISTRIBUTION OF 1,014 DISRUPTIONS OF MUSCLES AND TENDONS BY SITE AND TYPE OF INJURY*

UPPER EXTREMITY	PER CENT
Lacerations (540)	
Flexors, fingers	38.5
Extensors, fingers	26.4
Extensor pollicis longus	7.2
Flexor pollicis longus	5.4
Multiple tendons, nerves, vessels	5.0
Palmaris longus	3.1
Flexor carpi ulnaris	3.1
Flexor carpi radialis	1.8
Abductor pollicis longus	1.8
Extensor pollicis brevis	1.4
Thenar group	1.3
Biceps brachii	1.1
Brachioradialis	0.9
Extensor carpi ulnaris	0.7
Extensor carpi radialis, longus and brevis	0.7
Triceps brachii	0.7
Brachialis	0.4
Hypothenar group	0.3
Interossei	0.2
Direct trauma (136)	
Musculotendinous cuff	65.4
Extensors, fingers	16.9
Biceps brachii	11.8
Flexors, fingers	2.9
Triceps	1.5
Flexor pollicis longus	0.7
Extensor pollicis longus	0.7
Stress rupture (106)	
Musculotendinous cuff	54.7
Biceps brachii	26.4
Flexors, fingers	6.6
Extensor pollicis longus	5.7
Extensors, fingers	3.8
Triceps	1.9
Flexor carpi radialis	0.9
Miscellaneous (74)	
Musculotendinous cuff	47.2
Biceps brachii	25.8
Extensors, fingers	18.9
Extensor pollicis longus	6.8
Palmaris longus	1.3

LOWER EXTREMITY	PER CENT
Direct trauma (21)	
Quadriceps	100.0
Lacerations (58)	
Extensors, toe	27.7
Anterior tibial	17.3
Tendo achillis	17.3
Quadriceps	13.8
Flexor hallucis longus	5.2
Peroneus tertius	3.4
Peroneus longus	3.4
Posterior tibial	3.4
Adductor hallucis	1.7
Gracilis	1.7
Adductors, thigh	1.7
Hamstrings	1.7
Sartorius	1.7
Stress rupture (52)	
Quadriceps	42.4
Tendo achillis	23.1
Triceps surae	23.1
Hamstrings	3.8
Obturator internus	1.9
Pyriformis	1.9
Adductors, thigh	1.9
Posterior tibial	1.9
Miscellaneous (12)	
Triceps surae	75.0
Quadriceps	25.0

TRUNK	PER CENT
Direct trauma (2)	
Rectus abdominis	50.0
Intercostals	50.0
Stress rupture (12)	
Left hemidiaphragm	50.0
Trapezius	16.7
Rectus abdominis	8.3
Intercostals	8.3
Serratus anterior	8.3
Pectoralis minor	8.3
Miscellaneous (1)	
Sternomastoid	100.0

*Disruptions for each group indicated in parentheses.

In Group 1 (lacerations) there were no injuries to the musculotendinous cuff of the shoulder, but in each of the other three groups this structure was disrupted more often than any other (Table IV). Of 182 tears of the cuff, 19.7 per cent were not associated with injury either directly to the shoulder or indirectly via a fall on the outstretched arm; 48.9 per cent were due to direct injury to the region of the rotator cuff. In 10 instances tears of the cuff were associated with dislocations of the humeral head, and these were grouped with the direct injuries. Disruptions involving both the biceps and the musculotendinous cuff occurred in 15 cases. One-third of these were not associated with any known history of trauma, and approximately one-half occurred after a direct blow to the shoulder.

The biceps brachii ranked among the top three structures in number of disruptions in all groups except that of lacerations. The long head of the biceps was the usual site of disruption; however, there was one case of rupture of the short head. No history of injury could be obtained in 27.5 per cent of the instances in which the biceps was disrupted, and in 40.6 per cent the disruption was due to indirect (stress) trauma. One patient ruptured the long heads of both biceps brachii while lifting 400 pounds.

Previous fractures about the wrist had occurred in 8 of 11 stress ruptures and miscellaneous injuries of the extensor pollicis longus tendons. Seven disruptions were associated with Colles' fracture, and one with Barton's fracture. No history of any type of injury could be elicited in 2 cases, and one disruption occurred while the patient was playing a game of curling. Of 14 disruptions of the extensors of the fingers in Group 4 (miscellaneous), three were associated with previous injuries of the wrist or hand, nine occurred spontaneously or were of unknown cause, and two were associated with normal activity.

Disruptions in Lower Extremity.—The quadriceps femoris was the most frequent site of disruption in the lower extremity. Of 54 disruptions of this structure, 40.1 per cent were due to indirect (stress) trauma and 38.9 per cent to direct trauma. The quadriceps mechanism accounted for all of the disruptions due to direct injury and almost half of those due to indirect injury. Slightly more than one-third of these disruptions were in the patellar ligament, while more than one-half were in the quadriceps tendon and its lateral expansions. One patient ruptured both quadriceps tendons simultaneously when he fell from a high stairway. Another patient ruptured both tendons within 2 days in two separate falls. Manipulation of the knee 1 month after patellectomy accounted for one rupture of the quadriceps tendon.

Rupture of the tendo achillis occurred approximately one-half as frequently as did rupture of the quadriceps mechanism. More than 50 per cent of ruptures of the tendo achillis were due to indirect injury, and the remainder were due to lacerations. The tendo achillis ranked second in frequency among the indirect (stress) ruptures and third among the lacerations. Eight disruptions occurred while the patient was running or jumping, but there was no history of direct injury.

At the time of diagnosis it was thought that the plantaris muscle and tendon accounted for two-thirds of the disruptions of the triceps surae; the gastrocnemius and soleus muscles accounted for the remaining one-third.

More than 50 per cent of disruptions of the triceps surae were due to indirect (stress) injury, while in 42.8 per cent no history of injury could be elicited. This group of muscles accounted for three-fourths of all disruptions of the lower extremity in Group 4 (miscellaneous).

Disruptions in Trunk.—There were no lacerating disruptions of the musculature of the trunk. The left hemidiaphragm, which was the site of slightly less than 50 per cent of the ruptures, was of didactic interest. All traumatic diaphragmatic hernias were associated with multiple fractures, usually incurred in auto accidents. Most of these hernias were not discovered until many weeks after the original injury.

PROBABLE PREDISPOSING FACTORS

In 87 or 8.7 per cent of all the cases reviewed, factors which probably predisposed to muscle-tendon disruption were present (Table V). Tendinous calcification accounted for approximately one-third of the total number, as did osteoarthritis. The single case of tumor was that of a capillary hemangioma of the humeral head associated with an incidental tear of the shoulder cuff.

TABLE V. PREDISPOSING FACTORS

FACTOR	CASES
Tendinous calcification	28
Osteoarthritis	27
Old fracture	10
Idiopathic roughening or deformity of bone	10
Spurs and exostoses	7
Rheumatoid arthritis	2
Tuberculous tenosynovitis	2
Tumor	1
Total	87

The small number of disruptions due to rheumatoid arthritis is probably not truly representative. One of us (Lipscomb) has seen 4 spontaneous ruptures of tendons in the hand in the last 6 months as a result of rheumatoid arthritis; three were ruptures in the same person. With increased awareness, the diagnosis is probably being made more often now than in the 10-year period encompassed by this report.

COMMENT

Of 1,014 disruptions of tendons and muscles encountered at the Mayo Clinic in the period 1945 to 1954, inclusive, 598 were due to lacerations. Much has been written about the best means of handling lacerated tendons, but it is not the purpose of this or subsequent papers to elaborate further on the care of such injuries. Also the 15 disruptions of the musculature of the trunk will be eliminated from further study. As our population ages, we can expect to

see increasing numbers of ruptures of muscles and tendons due to the degenerative phenomenon. Therefore, in subsequent papers we shall present an analysis of the remaining 401 cases of disruption of tendons and muscles resulting from nonlacerating injuries. In this analysis we shall consider why these ruptures occur, what might be done to prevent them, and how they can be best treated. The first of the two papers to be published subsequently will deal with disruptions in the upper extremity, and the second with disruptions in the lower extremity.

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SOME PROBLEMS IN FLEXOR TENDON HEALING

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EARLY in his investigations of flexor tendons, Dr. Sterling Bunnell described a gliding mechanism for tendons pulling in a straight line differing from the one for those acting around corners. The coiled elastic fibers and soft fat surrounding straight tendons contain a disorganized system of blood vessels and lymphatics which enter and leave the tendon at random, an arrangement which Dr. Bunnell called paratenon.[1] Where tendons act around corners through a lubricated sheath, the blood vessels are organized into a mesentery attached to the volar surface. In spite of entirely different supporting structures, surgeons have persisted in trying to repair sheath-enclosed tendons with paratenon-nourished grafts. We raise the question of whether consistently poor results following repair of flexor tendons within the digital sheath may not be partly due to the notion that tendons are static adynamic structures which can be indiscriminately moved with no regard for their blood supply. If the importance of blood supply can be established, it next seems logical to question whether a paratenon-nourished graft such as the palmaris longus can be expected to function adequately in place of a lubricated sheath mechanism. We have attempted to answer some of these questions by studying the circulation to normal tendons and healing grafts and by observing the behavior of a composite tissue heterograft of the entire flexor mechanism.

In previousdly reported experiments a study was made of the relative effectiveness of blood vessels entering the ends and center of long tendons.[4, 5] Radioactive phosphorous tracer experiments revealed that vessels entering at the ends were no larger or more numerous than the intrinsic vessels and were unable to nourish more than the proximal or distal one-third of the tendon. Importance of the vessels nourishing the central third can be shown in several ways. C^{14} glycine turnover measurements performed by Neuberger and Slack and respiratory quotients determined in our laboratory reveal a small but measurable metabolic activity in tendon.[3] Direct evidence for the importance of central vessels was obtained by denying tendons this portion of their blood supply: in some experiments by wrapping plastic film around the tendons, and in others by severing the vessels daily with a circular subcutaneous knife.

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In each instance the center eventually became necrotic, indicating that diffusion of gases and nutrients without an actual vascular connection will not suffice.

We postulate that tendon transfers and free grafts heal somewhat like free split-thickness skin grafts. Because of a low metabolic rate (0.1 microliters of oxygen per unit weight per hour), they can survive 3 to 4 days under favorable circumstances by diffusion of gases and nutrients from the host. The largest aggregation of cells in a tendon is to be found in the visceral layer of the sheath which is, of course, in direct contact with capillaries of the host. For complete success, particularly if gliding function is to be preserved, vessels of the graft must actually join vessels of the host, including the intermediate segmental vessels as well as those entering from either end. Successful shielding of the graft by a mechanical barrier so that postoperative adhesions cannot form produces necrosis in the center of the graft. Grafts which survive and retain the properties of a normal gliding tendon are nourished by fibrous adhesions. The elasticity and attenuation of adhesions is variable, just as the character and amount of scarring varies in individuals, and may offer one reason why some grafts eventually glide after a period of active exercise. On the other hand, there is the familiar experience of performing a technically perfect graft in a cooperative patient only to find the graft solidly incarcerated in dense, unyielding cicatrix. Such patients may be comparable to those who, following surface restoration, develop superficial hypertrophic scars.

Experiments, such as the ones described, discourage further search for a substance to wrap around tendon grafts. It becomes apparent that, if by this means adhesions are successfully avoided, the result may prevent healing at the ends and will produce necrosis in the center. This observation, perhaps, is the only immediate contribution of our vascular experiments to the technique of free grafting. In other types of flexor tendon repair occasional opportunities arise to use the principles of segmental blood supply in a more positive fashion. Two examples are shown in Figs. 1 through 4.

The first patient sustained a laceration of the flexor profundus tendon to the long finger at the level of the mid-proximal phalanx. Three weeks after injury the proximal profundus tendon was advanced to the terminal phalanx by dividing it at the wrist and inserting the distal portion as an interposition graft. The coiled, elastic mesotendon and vincula are long enough to permit advancement while still preserving the intermediate blood supply. The value of not violating the central tendon attachments may have been manifest in a normal amplitude of motion only 10 days after removal of the pull-out wire.

In the second case, a tendon transfer was needed to supply adduction to the thumb. All of the sublimus muscles were paralyzed secondary to a high level median and ulnar nerve palsy. Nevertheless, the paralyzed ring sublimus tendon was transferred beneath the flexor tendons in the palm to the first metacarpal. It was then empowered at the wrist by the flexor carpi ulnaris which was functioning normally. The final result is shown in Fig. 4.

The same result might have been obtained by lengthening the flexor carpi ulnaris with a free graft, but in this instance a normal amplitude of motion was present almost immediately, and preserving the intermediate blood supply may have avoided some of the complications of a free graft. Although the evidence is strong that either preservation of intermediate vessels, as in these cases, or re-establishment of the vessels through adhesions around a free graft is necessary for survival, not enough is known about lubrication and gliding to form definite ideas concerning the relative importance of any one blood vessel group.

Fig. 1. Fig. 2.

Fig. 3. Fig. 4.

Fig. 1.—Preoperative view of lacerated flexor profundus tendon to long finger.

Fig. 2.—Postoperative view 3 weeks following advancement of flexor profundus tendon to distal phalanx.

Fig. 3.—Typical "claw hand" with adductor paralysis following combined median and ulnar nerve palsy.

Fig. 4.—Restoration of adduction in hand shown in Fig. 3 following fusion of first and second metacarpophalangeal joints and transfer of ring sublimus tendon to adductor of thumb.

Confronted with the evidence that fibrous adhesions transport blood vessels of vital importance, we next reasoned that their undesirable binding effect might be overcome by causing them to form where motion is not required. With such an objective in mind we have been experimenting with a composite tissue graft of the entire digital flexor mechanism which includes both flexor tendons, the vincula, and the coiled blood vessels or mesotendon

within an intact sheath. Theoretical advantages of such a graft are as follows. Removing the flexor mechanism as a complete unit permits the specialized coiled elastic vessels in the mesotendon to be transferred intact between the sheath and tendons. Normal wound healing with its binding fibrous components should occur between the transplanted sheath and host tissues instead of between the host tissues and the tendons as in a conventional graft. Success of the graft, therefore, depends upon the transplanted intrinsic vessels functioning between external vascular adhesions and the new tendons.

It is important to remove the graft without entering the tendon sheath at any point. The sheath varies in thickness along its course, and the operator must be exceedingly careful in the thin areas between pulleys. The most difficult part of the dissection is removing the graft posteriorly from the phalanges and interphalangeal joints; consequently an accurate knowledge of the various attachments of tendons and sheath to periosteum is mandatory. Of great value in preparing to remove the graft is the precise descripition of the flexor mechanism and its attachments by Dr. Emanuel Kaplan in his recent text.[2] Since the dissection must proceed in a subperiosteal plane between bone and tendon sheath, special care is required at the points of insertion of the tendons and vincula. At the joints it is best to remove the volar cartilaginous plates with the graft. Fig. 5 shows the technique of removing the graft.

Fig. 5.—Removal of composite tissue homograft of flexor mechanism without entering sheath.

Our first transfers were autogenous transplants in the fingers of monkeys. The grafts are unusually difficult to remove from a monkey's finger because of the size and hyperextensibility of the interphalangeal joint. They can be transferred, however, and will continue to glide and secrete synovial fluid following transfer to another finger. The most discouraging aspect of transfer from one finger to another was our inability to immobilize a monkey's

hand satisfactorily during the period of end-to-end tendon healing. Monkeys are so ferocious and clever in removing all types of fixation that it was seldom possible to transfer a graft between fingers and demonstrate activation of the grafted finger.

Human grafts were studied by transplanting the flexor mechanism from fresh cadavers to the abdominal wall of dogs. Heterotransplantation did not appear to effect the function of 12 grafts which were followed for varying periods up to 7 months. An autolyzing, allergic-type reaction was not observed in any of the human-to-dog transplants, and, to the contrary, tissue reaction around the grafts was no greater than around tendon autografts (Fig. 6). The vessels in the mesentery contained unclotted blood and a repeat of the previously described radioactive phosphorous transport studies demonstrated the effectiveness of transplanted vessels in nourishing the tendons. Furthermore, a normal amount of synovial fluid was found within the sheath and radioactive phosphorous could be detected in the fluid following a previous systemic injection. The mechanism of phosphorous transport across the sheath into synovial fluid is not known; we have no evidence that this is dependent upon an intact intrinsic circulation.

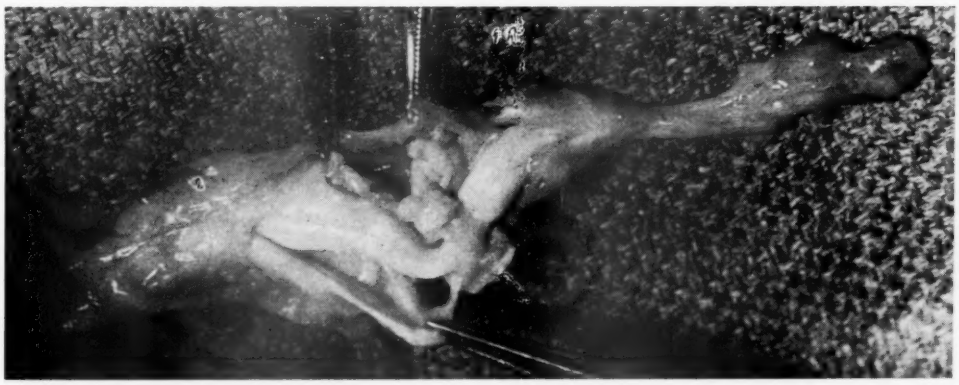

Fig. 6.—Composite tissue homograft incised 6 months following transfer beneath the abdominal wall of a dog. Note absence of adhesions within the sheath.

Apparently, the typical allergic type of autolysis which characterizes the destruction of epithelial homografts does not occur in fibrous tissue grafts, and it is particularly surprising that blood vessels remain patent, since an early sign of impending death in skin homografts is intravascular clotting and intimal destruction. Composite tissue tendon grafts stored at 37° F. in buffered salt solution and antibiotics for 7 days still showed respiration in the Warburg apparatus and could be successfully transplanted. Grafts refrigerated over 10 days did not respire in the Warburg apparatus and two such grafts were replaced by fibrous tissue after transplantation. Infection will cause tendon grafts to be absorbed and whether this accounts for disappearance of grafts after prolonged storage or whether transfer of living fibroblasts is necessary for survival is not clear at this time. Experiments are in progress to elucidate this important point.

Encouraged by the above results we selected a suitable human patient on whom to test the graft as a flexor tendon restoration. Preparation of the

recipient bed requires sacrifice of the sheath and pulleys, and, since the tendon homograft reaction in human fingers was unknown, we wanted a finger so badly damaged that repair by conventional autograft would likely fail. An additional reason for desiring an almost irreparably damaged finger was the possibility of a justifiable amputation if the proposed graft was a failure, thus, providing an opportunity for further study. The patient shown

Fig. 7.

Fig. 8.

Fig. 7.—Preoperative view of index finger damaged by electric fan 6 months prior to operation. Volar scar at base of flinger represents site of flexor tendon lacerations and subsequent tenosynovitis. Forced passive flexion demonstrates interphalangeal joint stiffness.

Fig. 8.—Operative view of finger shown in Fig. 7. Note radial digital nerve crossing skin flap in center of wound. Forceps point to periosteal tags which will be retained to anchor graft.

in Fig. 7 fulfilled many of these requirements. Six months before operation she sustained multiple dirty lacerations at the base of the index finger. Both tendons and the radial digital nerve were divided. Since the wound became infected and healed secondarily with a great deal of surrounding scar formation, primary repair of the tendons had not been attempted. No active

motion was possible distal to the metacarpophalangeal joint and sensation was diminished. The interphalangeal joints retained only half of their normal range of motion, and passive flexion was possible only to the degree demonstrated in Fig. 7. When the finger was opened through a mid-lateral incision, the entire sheath, tendons, and mesotendon were inseparably congealed in a dense fibrous cicatrix obliterating the synovial cavity. The soft tissue of the palm was also replaced by dense fibrous cicatrix and the proximal tendons had almost no "give" when stretched.

Fig. 9.—Postoperative view of hand shown in Fig. 7. Functional view with metacarpophalangeal joint blocked to demonstrate 45 degrees active flexion in interphalangeal joints.

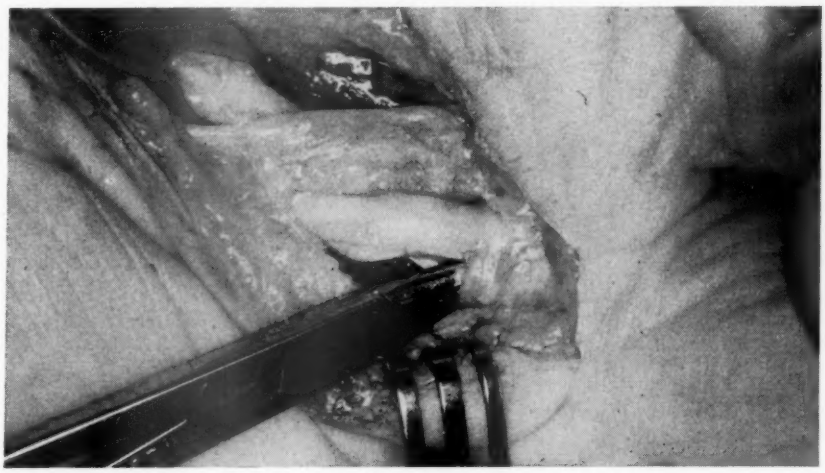

Fig. 10.—Operative view of composite tissue homograft 3 months following transfer. The hemostat is demonstrating the beginning of the sheath at the level of the metacarpophalangeal joint.

The entire sheath and both tendons were excised, including the periosteum over the volar surface of the phalanges. The graft was attached to periosteal tags along the full length of the finger and an end-to-end anastomosis at staggered levels was performed on both sublimus and profundus tendons. The volar cartilage plates were retained to prevent entering the joints, and, since the donor cartilages remained on the graft, the finger was thicker over the joint areas after the wound was closed. The patient had a smooth convalescence and the skin healed without complications. Four weeks

after operation the posterior splint was discarded to allow unlimited active and passive exercise. Only a slight flicker of motion was observed initially, but within 2 weeks the graft was functioning to the extent of providing approximately 45 degrees of flexion (Fig. 9). Furthermore, the only detectable point of attachment was at the inferior end of the palmar scar.

Six weeks later the palm was explored and the tendons appeared normal. Fig. 10 shows the intact sheath in the distal end of the incision, and, although normal motion was present immediately following lysis of the proximal adhesions, a full range of motion was not permanently restored. Perhaps the grafts should have been prolonged into the wrist where unavoidable adhesions at the proximal suture line are less restrictive.

Nine months following re-exploration, the finger flexes actively to within 2 cm. of the distal palmar crease (Fig. 11). This amount of flexion represents the full extent of passive motion allowed by the damaged joints. We feel that active flexion 9 months following transfer of the graft is evidence of permanent homograft survival.

Fig. 11.—Postoperative view 9 months following transfer of composite tissue homograft of the flexor mechanism.

Composite tissue homografts of the flexor mechanism are not yet being recommended as the method of choice for repairing all flexor tendon injuries within the digital sheath. Our early experiments have shown, however, that such grafts are tolerated well and may be utilized in situations where extensive sheath and overlying soft tissue destruction makes successful repair impractical by conventional autograft.

SUMMARY

We have reported the high spots from a group of experiments designed to reveal a suitable method for investigating and controlling tendon adhesions. Methodology and the bulk of data for the early vascular experiments have been published in detail elsewhere. The objective of this paper

has been to describe a few early experiments in restoring normal flexor tendon sheath and specialized blood supply by the use of a composite tissue homograft of the entire flexor mechanism. Composite tissue heterografts of the flexor mechanism from human cadavers persist following transplantation beneath the abdominal wall of animals. Composite tissue homografts can be transplanted successfully between human beings and be utilized to restore flexion to a severely damaged digit. A single example of a functioning human homograft of the flexor mechanism is described.

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IODIDE-INDUCED GOITER

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THE action of iodine as a goiter preventive in the form of iodized salt has been known since the beginning of the century. The therapeutic effect of Lugol's solution in cases of Graves' disease was described by Plummer in 1923.[10] In 1952 Bell[2] reported that, in a number of asthmatic patients with previously normal thyroids, prolonged use of iodides was followed by goiter formation and myxedema.

On the basis of 5 cases, Bell described the syndrome of simple goiter and myxedema as the result of prolonged use of iodides, which had been given in the form of syrup of hydroiodic acid, potassium iodide, or Lugol's solution. A comprehensive review of the literature on this subject can be found in the papers by Turner and Howard,[15] Rubinstein and Oliner,[11] and in the recent report by Bell,[1] with the detailed findings of the I^{131} uptake and protein-bound iodine levels. Most of the cases previously reported show a low uptake of I^{131} and a low protein-bound iodine level. When iodide administration is discontinued, rebound phenomena of the abnormal I^{131} uptake and the protein-bound iodine level took place but the values eventually returned to normal.

CASE REPORTS

Gold.—D. B. was a 40-year-old Negro typist. She presented with a large horseshoe-shaped goiter of 6 years' duration. In the course of preoperative observation, the goiter grew and the patient experienced choking on swallowing. There was puffiness of the eyelids and coldness of the finger tips. No history of a goitrogenic substance was obtained. The preliminary diagnosis was "Hashimoto's thyroiditis." The basal metabolism rate was −18 per cent. For 28 weeks cortisone, approximately 20 mg. per day, was administered with only temporary improvement. On March 24, 1955, bilateral subtotal thyroidectomy was performed with ligation of all 4 arteries and visualization of both inferior laryngeal nerves. In spite of careful dissection and ligation of all 4 major arteries, there was considerable bleeding from wide thin-walled vessels. Bleeding from the thyroid remnants was lively. At the conclusion of the operation, there was a drop in blood pressure to 50/20, which did not respond to intravenous glucose and whole blood. In spite of the low pressure, there was no tachycardia and no sweating. The pupils were contracted and respirations were easy, regular, 24 per minute. The shocklike condition responded promptly to hydrocortisone. It was thought to be an adrenocortical exhaustion syndrome due to the preceding cortisone medication. Under cortisone treatment the patient made an uneventful recovery and continued in excellent health. She was examined 12 months and 20 months after operation. There was no recurrence of the goiter. There were no signs of myxedema. The basal metabolism rate was +11 per cent. The body weight had risen from 99 to 165 pounds. Not until a year after operation did she reveal that for 20 years she had taken an anti-asthmatic preparation, Felsol. This had been the goitrogenic agent previously reported by

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Robbins, Maloof, and Oliner.[15] It contains antipyrine, iodopyrine, and citrated caffeine. Following operation the attacks of asthma ceased without further Felsol administration.

Twenty-seven cases of iodide-induced goiter had been reported before Jan. 1, 1958. There are two case reports with postmortem examination of the thyroid gland.

Morgans and Trotter.—A 66-year-old man was seen in 1950 with myxedema. For more than 10 years, for rheumatism, he had taken tablets containing a daily dose of 180 mg. of potassium iodide. Death a year later was caused by metastasis from a carcinoma of the colon and liver cirrhosis. At autopsy the thyroid presented a very uniform picture of large acini distended with colloid and lined by a flat epithelium. There was no lymphocytic infiltration.

Rubinstein and Oliner.—A 33-year-old woman was seen in September, 1954. She had taken antiasthmatic powders—Mendaco and Felsol—for the last 6 years because of severe asthma. Four years before admission, goiter and myxedema appeared. She died 3 months after admission during an asthmatic attack. At autopsy the thyroid follicles were of somewhat greater variation in size than is normally seen. The lining cells were low and cuboidal. There was an occasional papilla and minimal lymphocyte infiltration.

Only 4 cases had biopsies, all of which were taken during iodide administration. One of these 4, the second one of Turner's 2 cases, showed a struma lymphomatosa, a disease which is unrelated to the use of iodides and should therefore be excluded from the tabulation. There are, therefore, for review, only 4 cases including mine (Table I).

The following is a detailed description of the surgical specimen in my case. The specimen consisted of 2 lobes of a diffusely enlarged thyroid, with the corresponding parts of the isthmus. One measured 12.0 by 7.0 by 5.0 cm., and the other 9.5 by 9.5 by 4.5 cm. The anatomic configuration of the lobes was rather well preserved in spite of their huge size. They were gray, moderately firm, and lobulated, and did not show any nodules. (Fig. 1.)

The microscopic picture was uniform in both lobes and isthmus. There was diffuse hyperplasia with marked scarcity of colloid. The closely packed empty follicles varied in size and shape and were lined by typical tall cuboidal epithelium. There were numerous papillary projections. The papillary projections were of the regenerative hyperplastic type, not neoplastic. Some of the larger follicles show traces of thin colloid. The fibrous connective tissue septa were poor in fibrocytes and did not show congested blood vessels. Lymphoid tissue was almost completely absent. (Fig. 2.)

There was no histologic evidence of Hashimoto's struma nor of malignancy. Since the marked enlargement of the thyroid antedated the cortisone treatment, the goiter could not be related to this.

The microscopic picture in this case differs from Turner and Howard's description. There are unmistakable signs of lively epithelial proliferation. The tall cuboidal follicular epithelium is arranged in a single layer and covers multiple papillary projections which completely fill the interior of the individual follicles, enlarging them to a considerable degree (Fig. 3). The epithelial proliferation accounts for the enlargement of the gland. The changes must

TABLE I. IODIDE-INDUCED GOITERS WITH SURGICAL SPECIMENS

CASES*	AGE	SEX	MYX-EDEMA	GOITROGEN	DURATION ℞	OTHER THERAPY	OPERATION	FOLLOW-UP	PATHOLOGIC FINDINGS
Bell 1st series	11	F	No	Potassium iodide	5 years	No	Subtotal thyroid-ectomy	N.S.	Colloid-storage goiter, no hyperplasia
Bell 2nd series	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	Colloid-storage goiter with early adenomatous changes
Turner and Howard	8	F	+	Syrup of hydro-iodic acid	4 years	Desiccated thyroid, ½ gr. o.d. 1 yr. before operation	Subtotal thyroid-ectomy	Well under des-iccated thyroid	Multicystic gland, extensive hyperplasia with little or no colloid, tendency to papillomatous structures in hyperplastic area, no increase of lymphoid tissue†
Gold	40	F	+	Felsol	20 years	Cortisone 28 weeks before operation	Subtotal thyroid-ectomy	No return of goiter (off drug) nor of asthma	Huge diffuse goiter with extreme papillary hyperplasia

*One other case (Turner) with operation was found to have Hashimoto's struma and is not included.

†The authors state "the picture was similar to that seen in glands of patients receiving thiouracil and in those of goitrous cretins." (No photomicrographs.)

be considered as a response of the thyroid epithelium to the excess of circulating thyrotropin (TSH) unopposed by thyroid hormone, and are very striking. The complete absence of colloid morphologically confirms the lack of thyroid hormone in the gland. The effect of protracted preoperative cortisone treatment on the thyroid is unknown. There are no morphologic features of involution present. The whole clinical and microscopic picture is that of a progressive, diffuse, parenchymatous, hyperplastic goiter.

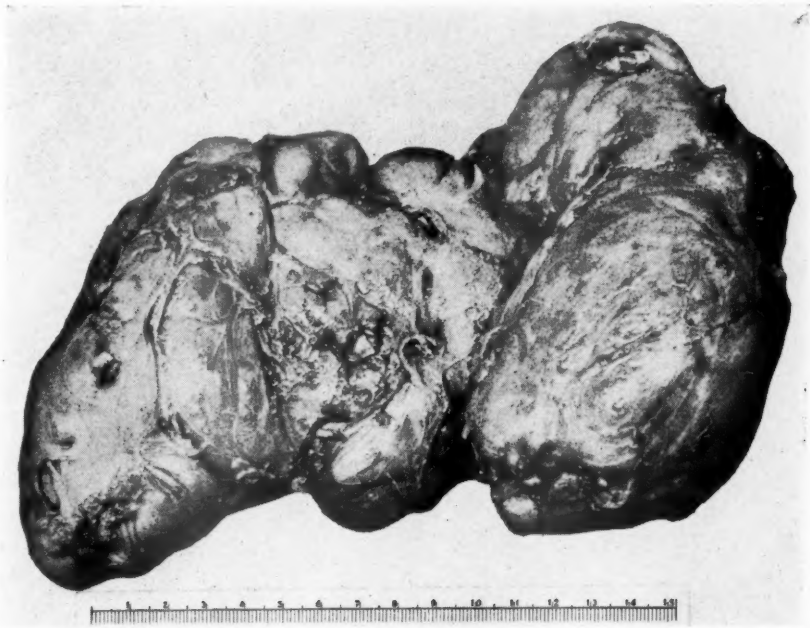

Fig. 1.—The operative specimen has been photographed showing the posterior surface. The right lobe, removed separately, has been approximated to the sectioned end of the isthmus. The ligated vessels at the right and left upper poles are apparent.

DISCUSSION

This histologic picture is different from that described by Albert Kocher as classical hyperplastic goiter of Graves' disease. In the thyroid of Graves' disease there are also papillary infoldings of the follicular walls covered by a single layer of tall columnar epithelium, but these are focal and less extensive throughout the gland. The follicles are lined by tall epithelial cells which may be multilayered with desquamation of the inner layer into the follicular lumen. The lumen contains thin colloid, which stains only slightly and shows signs of liquefaction by the scalloping of its edges. Lymphatic infiltration and lymph follicles are present. The interstitial tissue is not increased.

Series of clinical cases reported by Bell,[2] Turner and Howard,[15] and Turner[14] show a remarkable preponderance of adolescents. The ages ranged from 6 to 18 years. This is the age group in which characteristic changes in the thyroid have been found, which led to the description of adolescent goiter (jugend struma) by Gold and Orator.[5,6] Here the thyroid hyperplasia consists of numerous closed empty follicles which are arranged around branching

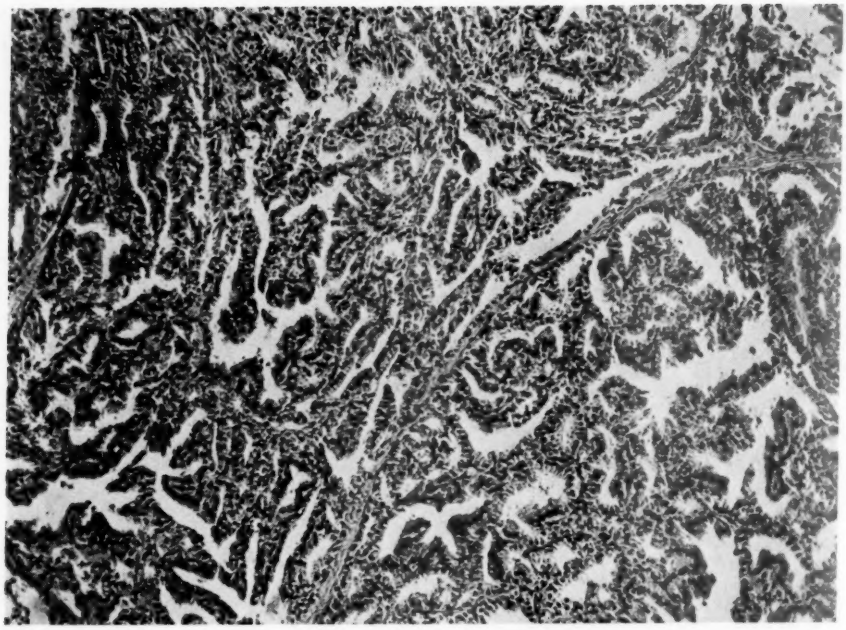

Fig. 2.—Photomicrograph showing a representative field. There is virtual absence of colloid with marked papillary hyperplasia. The epithelial cells are tall columnar. No focal collections of lymphocytes are seen.

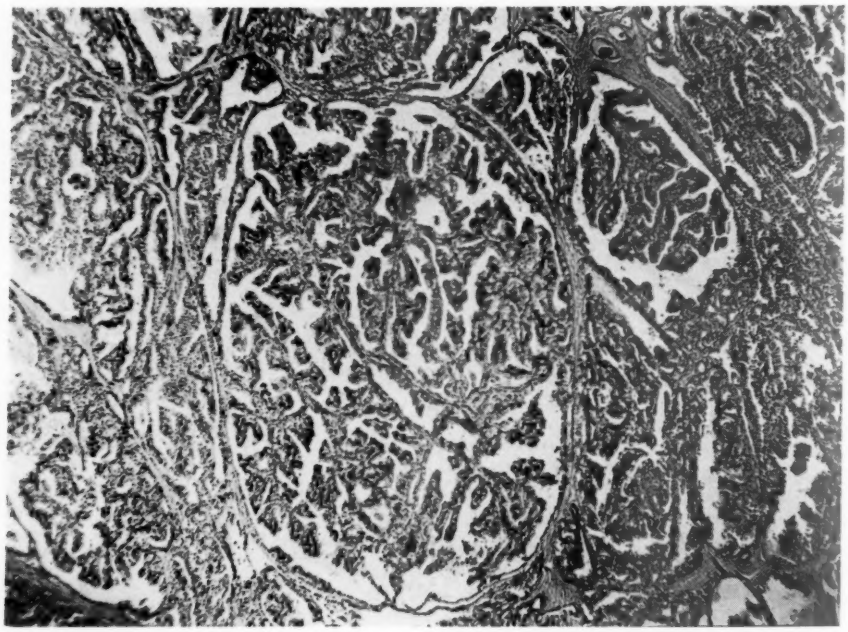

Fig. 3.—Photomicrograph showing papillary hyperplasia, which is extreme in the central focal area and one to the right, where stalked papillary processes are seen strongly suggestive of neoplasm. If such stalked papillary arrangement were found in an otherwise normal thyroid gland in one or more foci, it would almost certainly be considered neoplastic. In this diffusely hyperplastic gland it is probably wiser to consider these not neoplastic. The only proof of neoplasia under these circumstances would be the finding of metastatic foci outside the thyroid.

empty central canals lined by high epithelium. The quantitative iodine content of these glands was found by Homma[7] to be extremely low, 0.01 mg. per gram of thyroid tissue. Small amounts of iodine were able to convert these juvenile thyroids into normal colloid-containing glands, but they are probably very sensitive to higher doses of iodides which may result in myxedema (as in the case of Hurxthal) and goiter.

The papillary transformation of the entire gland in iodide-induced goiter differs from similar structures found in papillary carcinomas of the thyroid where the papillae are usually more irregular and loss of polarity of nuclei and mitoses are also present. Dunhill[4] has already stated that papillary formations in the thyroid are not confined to malignancies. They are seen in adolescent goiter. They are present to a greater or lesser extent in toxic goiter and in the experimentally produced brook-trout goiter of Marine and Lenhart. Papillary structures are, according to Dunhill, a typical response of the thyroid epithelium to physiologic or pathologic stimulation. He also quotes Wegelin who stated that one could not say with certainty where normal tissue ends and tumor tissue starts.

The stimulating factor in iodide-induced goiter is thyrotropin and it can be assumed that the same substance acts as a growth-promoting factor in at least the better differentiated forms of thyroid cancer of the papillary and follicular type. In recognition of the reciprocal action of TSH and thyroid hormone, Dunhill gave exogenous thyroid hormone in the form of desiccated thyroid to 2 children with metastases of papillary adenocarcinoma of the thyroid and obtained long-lasting suppression of the metastatic growths. One case was a child with onset of cancer at the age of 8, treated with desiccated thyroid at the age of 13. The second child's onset was at the age of 5 and metastases were found at the age of 24. In both cases the large metastases disappeared completely under thyroid treatment and the patients were still well 20 and 23 years after treatment was begun.

In 1955 Crile[3] reported on the follow-up of 5 patients with pulmonary metastases from papillary carcinoma of the thyroid and who had been treated after thyroidectomy with 2 to 4 grains of desiccated thyroid daily from 1 to 5 years. This was followed in all cases by improvement in the roentgenographic appearance of the pulmonary metastases and even complete disappearance of masses in the neck and chest. He also mentions 2 cases with bone metastases which showed arrest and recalcification during the treatment with thyroid and x-ray. In 1957 Crile reported on an additional number of cases with favorable response to thyroid treatment.

Thomas[12] also gives large amounts of thyroid (3 to 4 gr. daily) and more recently he also uses, with apparent success, L-triiodothyronine as a pituitary depressant when the suppressive action of desiccated thyroid begins to wane.

Frantz[12] quotes an observation of a patient who had been treated for a follicular adenocarcinoma by total thyroidectomy and I^{131}. A large solitary metastasis in the skull which had been present at the time of operation was treated with I^{131} without marked decrease in size. However, it became noticeably

smaller whenever the patient, who was a physician, gave himself large amounts of thyroid to combat the symptoms of myxedema which seemed unbearable to him. This observation suggests the hormonal dependency of the follicular type of thyroid carcinoma. At the same time it serves as a warning against the prolonged use of TSH and also perhaps of the thiourea drugs given in an effort to increase I^{131} uptake in the metastases of thyroid cancer.

SUMMARY

The majority of authors explain iodide-induced goiter as a blocking effect of the administered iodide on the synthesis of thyroxin within the thyroid gland, leading to myxedema. The goiter formation is explained as a response of the thyroid tissue to excess circulating thyroid-stimulating hormone (TSH) which remains unopposed by thyroxin. After discontinuation of the iodide medication, the thyroid gland may regress to normal or near normal size even without administration of thyroid hormone. This is the reason why so few cases have been submitted to operation. In the majority of cases desiccated thyroid has been given to treat the myxedema.

The reversible character of the syndrome under conservative treatment also supports the hypothesis given above to explain the pathogenesis.

The microscopic picture of my case of iodide-induced goiter is one of a progressive papillary transformation of the entire gland. It has led to the formation of a large hyperplastic goiter. The hyperplasia is explained by an excess of circulating TSH, which has acted upon the thyroid for many years unopposed by the iodide blocked thyroid hormone. It could be postulated that other cases not subjected to biopsy might well show a similar histologic picture.

Children and adolescents are predisposed to develop goiter and myxedema under the influence of long-continued iodide medication.

Based on the pathogenesis and the microscopic character of the iodide-induced goiter, the rationale of the treatment of metastases of papillary and follicular cancer of the thyroid with exogenous thyroid hormone is discussed.

Dr. Virginia Kneeland Frantz, of the College of Physicians and Surgeons, Columbia University, gave me continuous assistance and invaluable advice during the writing of this paper and has my special gratitude and appreciation. I wish also to thank Dr. H. H. Turner for the detailed report of his cases.

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THE ROLE OF THE HEMATOCRIT RATIO IN CIRCULATORY ARREST

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IF THE heart is resuscitated within a few minutes after acute circulatory arrest, an animal may survive the period of circulatory arrest with very little or no permanent destruction of cerebral tissue. If resuscitation is not attempted or is unsuccessful, the body undergoes destructive dissolution through biochemical and bacteriologic processes. Thus, following circulatory arrest, many changes occur, and, as the duration of circulatory arrest increases, more and more of these changes become capable of causing death after the circulation is restored.

The hematocrit ratio is a major factor in the resistance of animals to the development of irreversible hemorrhagic shock.[1] This effect is caused by the various effects of the hematocrit ratio on blood viscosity, oxygen-carrying capacity, and buffer capacity. Complete arrest of the circulation eliminates the effects of the hematocrit ratio on blood flow. Yet, the oxygen-carrying capacity and buffering capacity of the blood may be beneficial during the period of arrest. This study was initiated to determine the effect of variations in the hematocrit ratio on the survival rate and cerebral damage resulting from circulatory arrest of relatively long duration.

METHODS

Mongrel dogs, anesthetized by 30 mg. per kilogram of body weight of sodium pentobarbital, were subjected to circulatory arrest by a method described in previous publications.[2, 3] This method consisted essentially of ventricular fibrillation followed later by massage and defibrillation. All animals were given 3 mg. of heparin per kilogram of body weight 10 minutes before fibrillation. The dogs were selected on the basis of their hematocrit ratio, and 36 dogs with hematocrit ratios varying from 20 to 47 were obtained. A sample of blood was taken from the femoral artery before ventricular fibrillation, and the hematocrit ratio of this blood was determined by the method of Wintrobe.[4]

Two dogs were subjected to a different procedure. The heparinized blood from an arterial catheter was allowed to flow directly to the input of a Sharples continuous centrifuge. The plasma fraction of the centrifuged blood was returned to the animal via the femoral vein and additional plasma was injected to replace the volume loss resulting from the removal of erythrocytes. After the hematocrit ratio was below 2, the arterial catheter was disconnected from the centrifuge and the animal was allowed to bleed to death. Before expiration of

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a 75-minute period of arrest, the chest was opened and the trachea was catheterized. Cardiac massage and artificial breathing were initiated after 75 minutes of circulatory arrest, and 5 minutes later whole blood was injected into the animal. After the heart showed fibrillatory activity, defibrillation of the ventricles was effected by electric shock.

One week after the period of circulatory arrest, the surviving animals were classified according to the degree of cerebral damage. Those animals which could not survive in the presence of food and water were classified as severely damaged. Those animals capable of eating and drinking but presenting obvious cerebral impairment of any type were classified as moderately damaged. At the end of one week, some of the animals showed no outward sign of cerebral damage. These animals were classified as having no cerebral damage although pathologic and biochemical studies probably would have revealed some destruction of tissue.

Standard values of significance were used in describing the results.

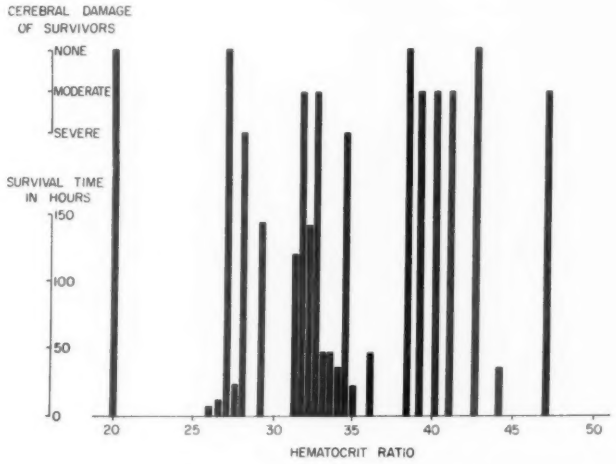

Fig. 1.—Ten minutes of circulatory arrest in dogs with hematocrit ratios varying from 20 to 47.

RESULTS

Ten Minutes of Circulatory Arrest.—Fig. 1 shows the results of subjecting 24 dogs to circulatory arrest of 10 minutes' duration. The hematocrit ratio of the animal is plotted along the abscissa and the duration of life or the condition of the animal one week after circulatory arrest is indicated along the ordinate. Survivals occurred in all ranges. In the hematocrit ratio range 20 to 35, 6 (37.5 per cent) of 16 dogs survived. In the hematocrit ratio range 35 to 50, 6 (75 per cent) of 8 dogs survived. The group with hematocrit ratios in the range 35 to 50 had a significantly higher survival rate than those in the hematocrit ratio range 25 to 35. A total of 12 dogs survived for one week. In the hematocrit ratio range 35 to 50, 2 dogs showed no cerebral damage and 4 showed moderate cerebral damage. In the range 20 to 35, 2 dogs showed no damage, 2 dogs showed moderate damage, and 2 dogs showed severe damage. These results do not significantly differ; however, the groups are too small for accurate analysis.

Fifteen Minutes of Circulatory Arrest.—Fig. 2 shows the results of subjecting 12 dogs to 15 minutes of circulatory arrest. In the hematocrit ratio range 20 to 35, 4 of the 8 dogs survived for one week. In the hematocrit range 35 to 50, there were no survivors. This difference is highly significant although the smallness of the groups may tend to exaggerate the analysis. Only one of the 12 dogs survived circulatory arrest of 15 minutes duration with no cerebral damage. One dog survived with moderate cerebral damage and two showed severe damage.

Seventy-Five Minutes of Circulatory Arrest.—Two dogs were subjected to 75 minutes of circulatory arrest after their hematocrit ratio had been decreased as previously described. Both animals were easily resuscitated. After resuscitation, the heart contracted vigorously, and the systemic blood pressure remained above normal for over an hour. Both animals attempted to breathe; however, neither was able to maintain breathing of a normal quality. One animal survived for 4 hours and the other for 2½ hours.

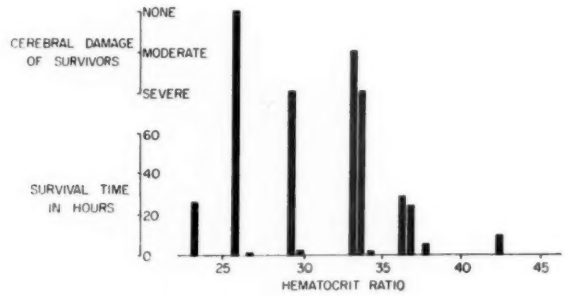

Fig. 2.—Fifteen minutes of circulatory arrest in dogs with hematocrit ratios varying from 24 to 43.

DISCUSSION

The results indicate that survival from 10 minutes of circulatory arrest may occur throughout the hematocrit ratio range 20 to 47. Furthermore, the extent of cerebral damage is not absolutely dependent upon the hematocrit ratio during the period of arrest. There is, however, a greater likelihood of survival in the higher hematocrit ratio range than in the lower range after 10 minutes of circulatory arrest.

Extension of the period of circulatory arrest to 15 minutes changed the survival pattern. The animals with hematocrit ratios in the range 20 to 35 showed a higher rate of survival than those in the higher range. Two dogs were prepared with essentially no cellular components. Although these animals did not survive permanently, they gave some indications that survival, at least, might be effected at this long range of circulatory arrest.

The present study indicates that the residual oxygen or the buffer capacity of the blood may be of some value during short periods of circulatory arrest, but as the period of circulatory arrest is increased, survival depends upon other factors. Furthermore, the hematocrit ratio range in which animals show the

greatest resistance to hemorrhagic shock (30 to 40) shows no consistent correlation with the hematocrit range in which animals are most resistant to circulatory arrest.

SUMMARY

Thirty-six dogs with hematocrit ratios varying from 20 to 47 were subjected to circulatory arrest of 10 or 15 minutes' duration. Those animals with hematocrit ratios in the range 35 to 50 showed a significantly higher survival rate after 10 minutes of circulatory arrest than those in the hematocrit ratio range 20 to 35. After 15 minutes of circulatory arrest, the survival rate of the animals was higher in the lower hematocrit ratio range.

Two animals with hematocrit ratios below 2 were subjected to 75 minutes of circulatory arrest. Both animals were resuscitated and both animals survived for several hours, exhibiting in particular vigorous cardiac contraction.

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RELATIVE SUITABILITY OF UROKON 70 PER CENT AND HYPAQUE 90 PER CENT FOR USE AS AORTOGRAPHIC CONTRAST MEDIA

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ANALYSIS of the physical properties of the various elements suggested the acceptability of iodine-containing compounds for use as angiographic contrast media. As early as 1923, sodium iodide was successfully employed clinically for roentgenographic visualization of peripheral arteries.[1] In 1929, this compound was injected into the abdominal aorta demonstrating the feasibility of aortography.[2] Concentrated solutions of sodium iodide gave excellent radiopacity, but their marked tissue toxicity prevented widespread use as angiographic contrast media. Ionizable or free iodide was incriminated as the basis for the toxic effects.[5, 6]

This suggested that organic iodine compounds might exhibit less tissue toxicity and still be suitable for use as contrast media. Several such compounds have been introduced during the past two decades. In recent years Urokon sodium (sodium acetrizoate) has been the contrast substance most frequently used for aortography in this country.[4] Toxic reactions to this compound, however, are well documented, and the need for a less toxic contrast medium of comparable radiopacity led to the development of Hypaque-M 90 per cent. The toxic effects and physical properties of Urokon sodium 70 per cent and Hypaque-M 90 per cent, as related to their use in abdominal aortography, have been investigated and presentation of the result of these studies comprises the substance of this report.

Investigation of the tissue toxicity of these two compounds has been limited to an evaluation of their effect on the spinal cord and kidney. Damage to these organs has been the cause of over 50 per cent of the serious complications resulting from the clinical use of Urokon sodium 70 per cent in abdominal aortography.[4]

METHOD

Spinal cord damage resulting from the aortic or lumbar arterial injection of contrast media was assessed. All injections were manually performed under direct vision at laparotomy (using sterile precautions) in anesthetized,

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Mallinckrodt Chemical Works (Urokon) and Winthrop Laboratories (Hypaque-M) generously supplied the contrast media used in this study.

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supine mongrel dogs. Anesthetization was accomplished with veterinary Nembutal (30 mg. per kilogram) except in two instances in which succinylcholine and endotracheal oxygen were used.

Aortic injections were standardized as follows. The anterior wall of the aorta was punctured with a No. 18-gauge needle 1 cm. below the origin of the left renal artery, and, with the tip of the needle slanted cephalad, 15 c.c. of medium was injected over a 5-second (± 1 second) period.

The first pair of lumbar arteries caudad to the origin of the left renal artery was selected for lumbar arterial injection. These arteries, with their corresponding aortic segment temporarily isolated from the circulation by appropriate application of Potts ductus clamps, were perfused with amounts of contrast medium varying from 2 to 30 c.c. The occlusion did not exceed 60 seconds. In all instances the contrast medium was introduced into the isolated aortic segment. Release of aortic occlusion was accomplished by first removing the superior ductus clamp and then the inferior clamp. This procedure insured lumbar artery reception of all of the injected material.

Hindlimb neurologic deficit was assessed following recovery from anesthesia. Those dogs showing impairment were observed throughout their postinjection survival (up to 5 weeks). At the time of demise or sacrifice, spinal cords from paraplegic animals were removed for subsequent microscopic examination. Tissue sections were prepared by the routine histologic techniques using hematoxylin and eosin stains.

Concomitant evaluation of nephrotoxicity was carried out in the aortic injection group of animals. Renal injury was estimated clinically by means of serial nonprotein nitrogen determinations while the tissue damage was surveyed by means of microscopic examination.

The relative radiopacity, viscosity, osmolarity, pH, solubility, and stability of Hypaque and Urokon were compared. Radiopacity was assessed by in vitro methods, while relative viscosity was determined by measuring the rate of flow of the media from a constant pressure injection device. The osmolarities were determined indirectly by comparing the appearance of hemolysis of red blood cells of known fragility when suspended in serial dilutions of the two media.

RESULTS

Neurotoxicity.—The neurologic injury resulting from aortic or lumbar artery injection of Urokon and Hypaque was assessed in 22 unselected mongrel dogs.

The results of aortic injection of the two media are illustrated in Fig. 1. The pattern of immediate response of those animals receiving Urokon was as follows: Usually within 30 to 45 seconds after injection hyperextension of the hindlimbs (progressing to myoclonic seizures) was noted. These seizures continued for 2 to 10 minutes and were followed by a transient period of hyperreflexia. The two animals injected under succinylcholine immobilization had no immediate motor response. Of those animals receiving aortic injections of Hypaque, only one transient hyperreflexia was observed (Table I).

TABLE I. IMMEDIATE AND ULTIMATE NEUROLOGIC RESPONSE TO AORTIC INJECTION OF 15 C.C. OF CONTRAST MEDIA

DOG	MEDIUM	IMMEDIATE RESPONSE			PARAPLEGIA
		HYPER-REFLEXIA	HYPEREX-TENSION	SEIZURE	
623	Urokon	+	+	Marked	+
630	Urokon	+	+	Marked	+
615	Urokon	+	+	Marked	+
689*	Urokon	–	–	None	+
713*	Urokon	–	–	None	+
670	Urokon	+	+	Marked	+
764	Hypaque	+	–	None	–
765	Hypaque	–	–	None	–
775	Hypaque	–	–	None	–
791	Hypaque	–	–	None	–
792	Hypaque	–	–	None	–
795	Hypaque	–	–	None	–

*Succinylcholine immobilization.

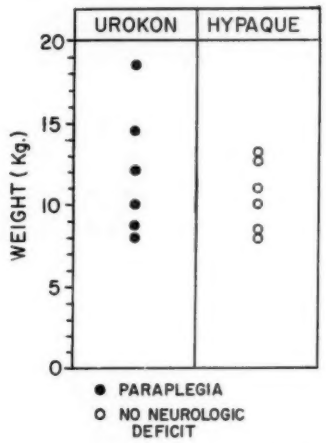

Fig. 1.—Neurologic deficit resulting from aortic injection of contrast media. Note lack of influence of animal weight.

TABLE II. IMMEDIATE AND ULTIMATE NEUROLOGIC RESPONSE TO LUMBAR ARTERY INJECTIONS OF VARYING AMOUNTS OF CONTRAST MEDIA

DOG	MEDIUM	AMOUNT	IMMEDIATE RESPONSE			PARA-PLEGIA
			HYPER-REFLEXIA	HYPEREX-TENSION	SEIZURE	
762	Urokon	2 c.c.	+	+	Mild	–
37	Urokon	2 c.c.	–	–	None	–
719	Urokon	2 c.c.	+	+	Marked	+
765	Urokon	5 c.c.	+	+	Marked	+
587	Urokon	5 c.c.	+	+	Marked	+
808	Urokon	15 c.c.	+	+	None	+
769	Hypaque	15 c.c.	+	–	None	–
836	Hypaque	30 c.c.	+	–	None	–
29	Hypaque	30 c.c.	–	–	None	–
36	Hypaque	30 c.c.	–	–	None	–

The immediate response and neurologic damage resulting from the segmental artery injections are tabulated in Table II.

Regardless of the technique of injection, there was no clinically apparent difference in the character of the paraplegia. The paralysis was characterized by flaccidity of the hindlimbs and loss of sphincter control. One animal

exhibited definite priapism which progressed to gangrene of the phallus. The nature of the paraplegia did not change with one exception, and in this instance the paralysis changed to a spastic form after 10 to 14 days. Of the 10 paraplegic animals only 5 survived more than one week. Four of the 5 animals surviving more than one week had received segmental artery injections.

The gross pathologic changes were neither consistent nor obvious but both myelomalacia and hyperemia of the lumbosacral cord were occasionally evident.

Microscopic lesions were limited to the region of the lumbar enlargement and sacral cord. No instances of primary cauda equina damage were encountered. Within the first week following neurologic damage, the gray matter exhibited necrosis with extravasation of red blood cells. There was engorgement of capillary and arteriolar vessels but minimal evidence of thrombosis. The neuronal and glial elements of the gray matter were completely destroyed in many instances with remarkable preservation of the myelinated long-column structures immediately adjacent (Fig. 2). The central canal often was the only identifiable landmark within the central cord. At the end of the first week and thereafter, up to 3 weeks, gitter cell infiltration of the necrotic gray matter was very pronounced (Fig. 3). As in the earlier lesions almost complete dissolution of the gray matter was encountered with preservation of the peripheral myelinated structures. There was, however, increasing evidence of axonal disappearance within these myelin tubes. Areas of hemorrhage were not commonly observed in the sections of the older lesions.

Nephrotoxicity.—Only 3 of the 6 animals receiving intra-aortic Urokon survived 48 hours. Nonprotein nitrogen values in these animals rose to abnormally high levels. No animal insulted similarly with Hypaque became uremic (Fig. 4).

No characteristic gross kidney lesions were noted irrespective of the degree of azotemia.

In those animals rendered uremic by Urokon, there was no microscopic evidence of thrombosis or loss of integrity of the blood vessels. The glomeruli in some animals demonstrated increased permeability by virtue of the appearance of a protein material in Bowman's space. Irregular and variable tubular damage was present ranging from a maximal injury characterized by dissolution of tubular epithelium and the presence of intraluminal proteinaceous material and cellular debris to a minimal change of cloudy swelling of the tubular epithelium (Fig. 5).

Physical and Chemical Properties.—The relative radiopacities are illustrated in Fig. 6. The viscosities of Urokon and Hypaque relative to that of water at varying temperatures can be ascertained from Fig. 7. The more viscid Hypaque-M 90 per cent, as opposed to Urokon 70 per cent, must be warmed prior to injection because of the presence of a crystalline precipitate on standing at room temperature.

Fig. 2.

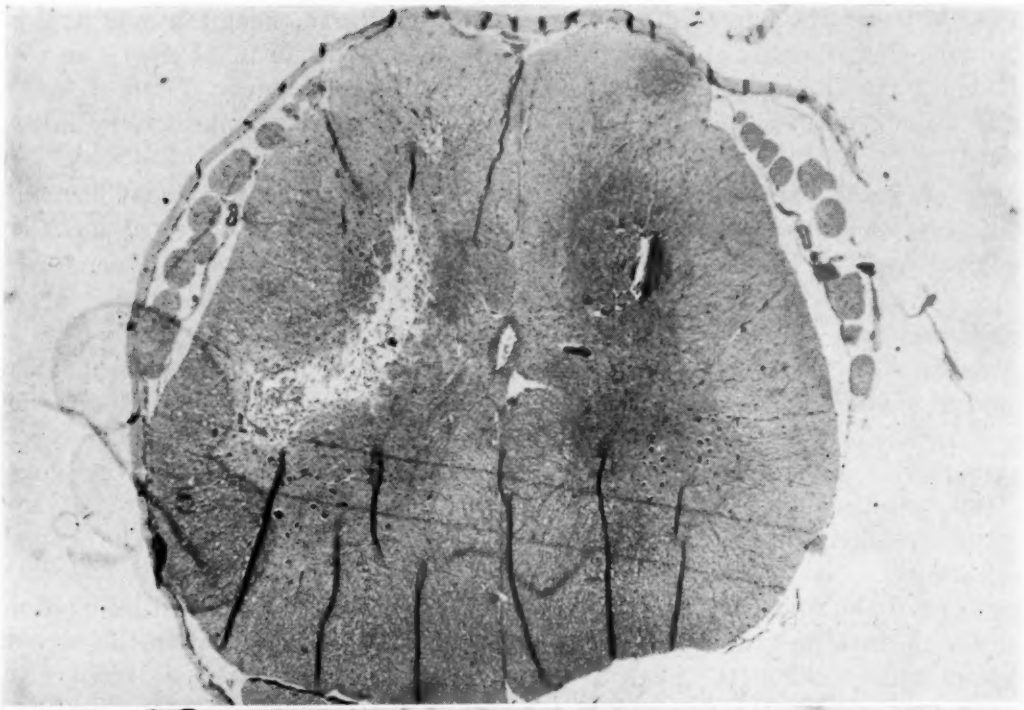

Fig. 3.

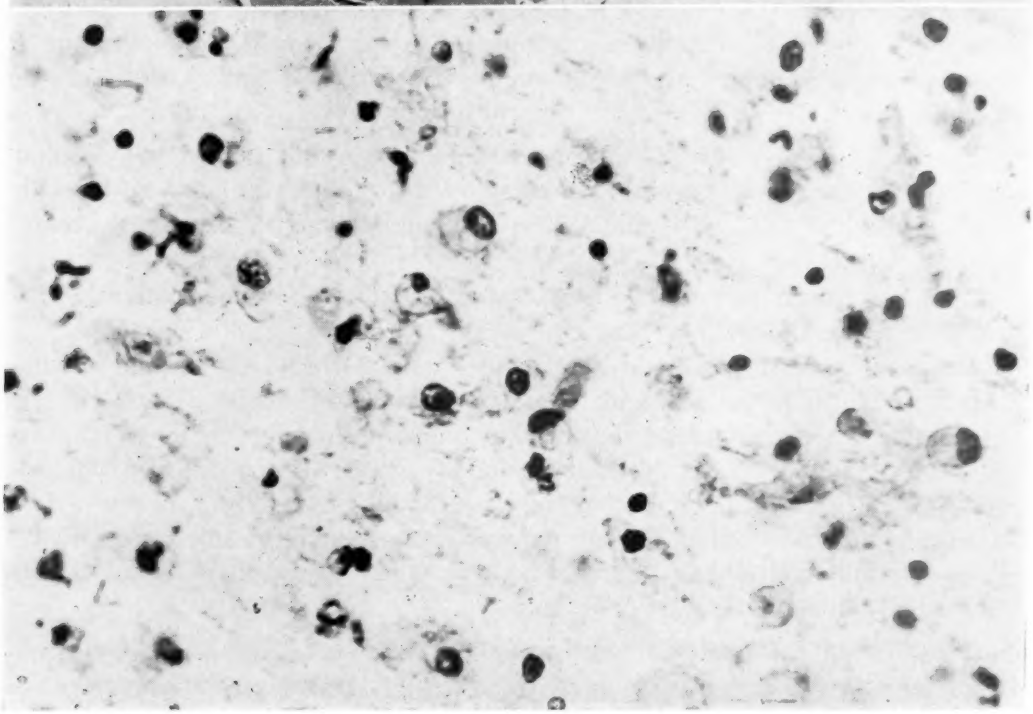

Fig. 2.—Photomicrograph (low power) showing unilateral dissolution of gray matter. Note preservation of myelinated columns.

Fig. 3.—Photomicrograph (×675, ⅛ off reduction) of spinal cord showing the gitter cell accumulation that occurs one week postinjury.

The pH of Urokon is 7.0 to 7.4, while that of Hypaque is 7.4.

The appearance of hemolysis of red blood cells suspended in serial dilutions of the two media and saline is depicted in Table III. The data in Table III indicate that the osmolarities of Urokon 70 per cent and Hypaque-M 90 per cent are essentially the same and are about 10 times that of normal saline.

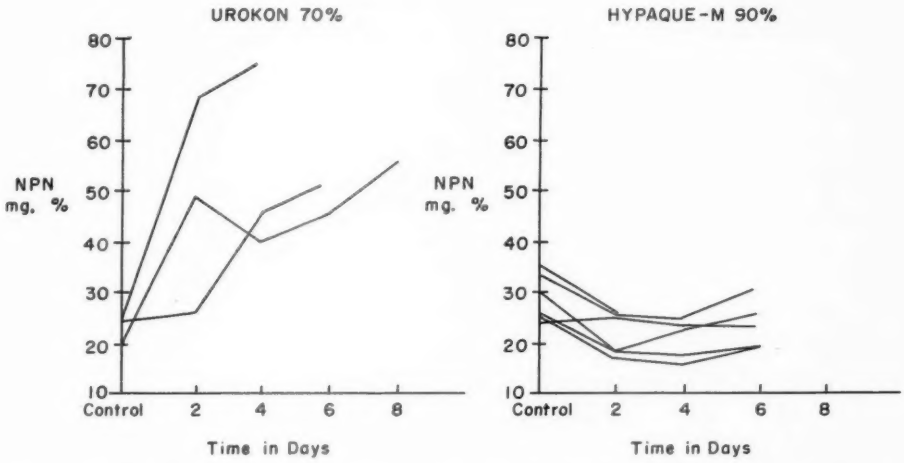

Fig. 4.—Nonprotein nitrogen values in animals receiving intra-aortic injections of Urokon 70 per cent or Hypaque-M 90 per cent.

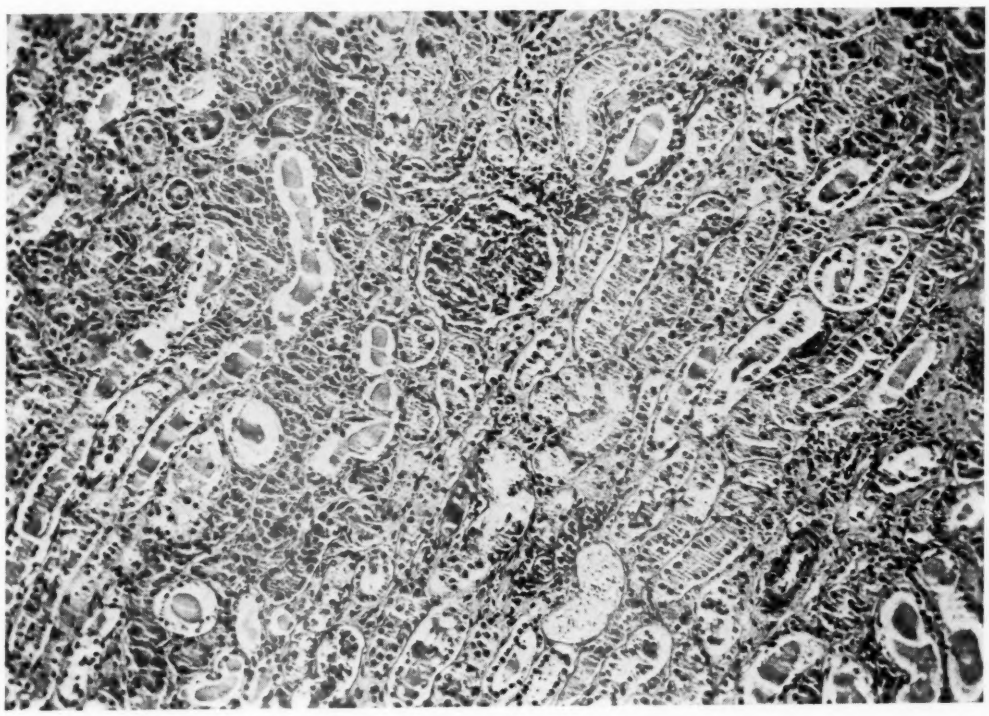

Fig. 5.—Photomicrograph (×150, ¼ off reduction) showing widespread derangement and destruction of tubular epithelium, intraluminal proteinaceous material and cellular debris. Glomerulus and blood vessels are intact.

Both of these organic iodides are equally sensitive to strong light with disassociation of iodine from the organic complex resulting from excessive exposure.

TABLE III. RELATIVE HEMOLYSING POTENTIAL OF SERIAL DILUTIONS OF SALINE, UROKON, AND HYPAQUE-M

CONCENTRATION (% W/V)		HEMOLYSIS		
DYE	SALINE	UROKON	HYPAQUE-M	SALINE
5	0.6	0	0	0
4.75	0.57	0	0	0
4.5	0.54	0	+	0
4.25	0.51	0	+	0
4	0.48	0	++	0
3.75	0.45	0	+++	+
3.5	0.42	+	+++	++
3.25	0.39	++	+++	+++
3	0.36	+++	+++	+++
2.75	0.33	+++	Complete	Complete
2.5	0.30	+++	Complete	Complete
2.25	0.27	Complete	Complete	Complete
2	0.24	Complete	Complete	Complete

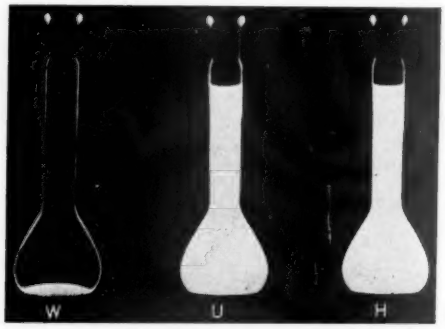

Fig. 6.—Relative radiopacities of water (W), Urokon 70 per cent (U), and Hypaque-M 90 per cent (H).

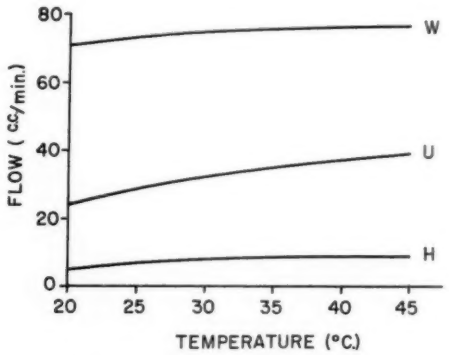

Fig. 7.—Relative flows of water (W), Urokon 70 per cent (U), and Hypaque-M 90 per cent (H) at varying temperatures from a constant low pressure injection system.

DISCUSSION

The acceptability of Urokon Sodium 70 per cent as an aortographic medium is generally acknowledged. However, greater experience with

aortic injection of this compound has been attended by an increasing awareness of the existence of a definite tissue toxicity, especially in regard to the central nervous system and the kidney.

The basis of Urokon injury has been ascribed to one or more of the following mechanisms: (a) tissue ischemia resulting from arterial insufficiency secondary to arterial spasm, (b) tissue necrosis resulting from arterial insufficiency secondary to arterial thrombosis, (c) structural alterations in the capillary endothelium leading to drastic chemical changes of the cellular environment, and (d) direct cytotoxic action.

The implication of the studies presented here is that the mechanism of Urokon injury to the spinal cord and kidney is a direct cytotoxic effect. This hypothesis is based upon the following evidence: (a) the myoclonic seizure simulates the central nervous system response to known nerve cell toxins, (b) clinical evidence of abnormal central nervous system irritability so promptly follows arterial dissemination of the Urokon that tissue anoxia as the primary cause of the nerve cell injury is precluded, and (c) no microscopic evidence of vascular wall damage or thrombosis in the areas of massive nerve cell and nephron necrosis was observed.

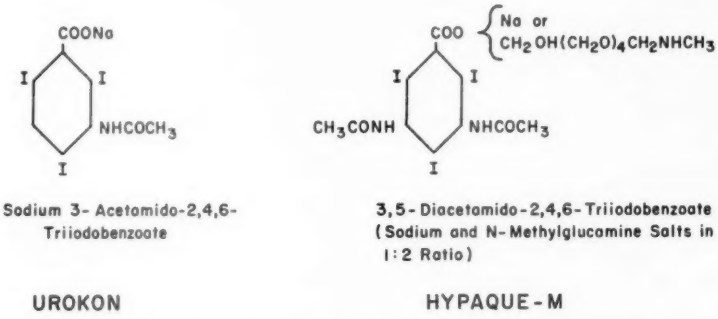

Fig. 8.—Structural formulas of Urokon and Hypaque-M.

The reason for the marked difference in tissue toxicity of Urokon and Hypaque-M is not known. It is interesting to note that the iodine contents of these two compounds are essentially the same. Urokon 70 per cent contains 461 mg. per cubic centimeter and Hypaque-M 90 per cent contains 462 mg. per cubic centimeter.

The toxicity would appear to be related to either a difference in chemical structure or a variation in physical characteristics. In Fig. 8, the structural formulas are shown. It is noted that the basic difference is the presence of a second acetamido side chain in Hypaque. This substitution in the ring may account for the relative lack of Hypaque toxicity. A further difference is that Hypaque-M 90 per cent is a 2 to 1 (by weight) mixture of the N-methylglucamine and sodium salts. It is possible that the N-methylglucamine radical offers a specific protective action similar to that ascribed to glucose by Kenan and associates.[3]

The only significant physical difference is the greater viscosity of Hypaque-M 90 per cent. This greater viscosity is important in that it makes

rapid injection more difficult and theoretically it increases the tendency of the dye to be carried as an axial bolus down the aorta. Therefore, perfusion of capillary beds supplied by laterally originating small arteries, such as the lumbar arteries, may be inhibited by this axial flow. The inability of Hypaque-M 90 per cent to cause paraplegia following direct lumbar artery injection would indicate that its lack of toxicity is not dependent upon these factors. However, it is conceivable that the greater viscosity is protective at the capillary level by preventing the critical temporal exposure of toxic concentrations to the susceptible cells.

CONCLUSIONS

Hypaque-M 90 per cent exhibits much less neurotoxicity and nephrotoxicity than Urokon 70 per cent.

The injury caused by Urokon seems to be on the basis of a cytotoxic mechanism.

The greater viscosity of Hypaque-M 90 per cent impairs its angiographic effectiveness when manually injected into the aorta through the small bore injection equipment used for translumbar aortography.

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FOLLOW-UP STUDY OF PATIENTS WITH ARTERIOSCLEROTIC ANEURYSM OF THE ABDOMINAL AORTA TREATED BY RESECTION AND FREEZE-DRIED HOMOGRAFT

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IN 1951, Dubost, Allary, and Oeconomos[10] performed the first successful resection with homograft replacement of an aneurysm of the abdominal aorta. Shortly thereafter, Bahnson,[1] Cooley and DeBakey,[6] and others reported successful instances of treatment of abdominal aneurysm by resection and grafting. In subsequent years an extensive experience with this procedure has been recorded by many clinics.[2, 3, 9, 13, 14]

A variety of arterial substitutes have been employed to restore continuity following aortic resection. Gross and his associates,[12] who revived interest in arterial grafting in 1949, presented a method of preservation of grafts in serum solution. Grafts preserved by freezing or freeze-drying had wide application during the years 1952 through 1956. In the past several years, many types of synthetic prostheses have been employed.

Early in 1954, an arterial bank was established at Vanderbilt University Medical Center. This bank has employed ethylene oxide sterilization of vascular segments and preservation by the freeze-dry method.[6] From April, 1954, through June, 1957, there were 40 patients with arteriosclerotic aneurysm of the abdominal aorta who were treated by aneurysmectomy and interpolation of a freeze-dried homograft. While plastic prostheses have tended to replace homografts in recent years, interest in the long-range behavior of freeze-dried homografts as aortic substitutes has prompted this study.

CLINICAL MATERIAL

All patients at the Vanderbilt University Hospital and Thayer Veterans Administration Hospital operated upon for aneurysm of the abdominal aorta with homograft replacement during the period of this study have been included. These patients have now been followed from 1 to 4 years. Surgeons of the attending and resident staffs performed the operative procedures. The Vascular Bank at Vanderbilt University Hospital recorded the data as they accumulated.

RESULTS

Vital Statistics.—There were 40 patients with arteriosclerotic aneurysm of the abdominal aorta. Each was treated by resection of the aneurysm and implantation of a freeze-dried homograft. The patients ranged in age from 37 to 81 years. The average age was 66 years. There were 2 women and 38 men.

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Presenting Complaint.—Thirty-one patients had symptoms referrable to the abdominal aneurysm, and the symptom duration averaged 10 months. There were 9 patients who were asymptomatic. The most common symptom was abdominal pain and this was the case in 23 of the 40 patients. The primary complaint of 6 patients was back pain, whereas hip pain was noted by two others. Five patients, who had been followed by a physician, were known to have had an abdominal aneurysm from 7 months to 3 years before operation. Two of these and 6 others had developed the catastrophic manifestation of rupture of the aneurysm and required emergency operation upon admission.

Coexisting Disease.—Thirty-two of the patients displayed evidence of other significant disease processes in addition to the aneurysm of the abdominal aorta. Of special note is the fact that 20 patients had hypertension, 5 patients had a previous history of myocardial infarction, and 4 patients had angina pectoris.

Physical Findings.—Twenty-six of the patients had a readily palpable, pulsatile abdominal mass at the time of admission. Of the 14 patients in which a definite pulsatile abdominal mass was not present, 4 had undergone previous laparotomy, in 5 the diagnosis was established by a plain abdominal x-ray, in 3 an abdominal aortogram revealed the diagnosis, and in 2 a ruptured aneurysm was discovered at the time of emergency laparotomy. The mass was located in the mid-abdomen in 14 patients, the right side of the abdomen in 7 patients, and the left side of the abdomen in the remaining 5 patients. In the 8 patients with ruptured aneurysms the manifestations of shock, abdominal tenderness, and palpable mass were present, although in two instances the mass did not seem to be pulsatile.

Special Studies.—A plain x-ray of the abdomen revealed the calcific outline of the aneurysm in 14 of the patients. An abdominal aortogram was performed in 11 patients and this demonstrated the aneurysm accurately in 9 instances. The serologic tests for syphilis were positive in 2 patients and negative in the remainder.

Operative Statistics.—The aneurysm was limited to the abdominal aorta in 23 patients and involved one or both common iliac arteries in the remaining 17 patients. In each of the 40 patients, the aneurysm arose below the renal arteries. Rupture of the aneurysm prior to surgical intervention had occurred in 8 instances. During the resection and grafting, the aorta was occluded immediately below the renal arteries for 1 to 2 hours with an average occlusion time of 1 hour and 36 minutes. A sympathetic blocking agent, Arfonad, was administered during the period of occlusion in the last 5 patients. Heparin (10 mg.) was injected distally into each iliac artery at the time of occlusion.

In each instance the entire aneurysm and the aortic bifurcation were resected. A freeze-dried aortic bifurcation homograft was reconstituted by immersion in sterile saline for 20 minutes. The homograft was sutured in place using 4-0 arterial silk proximally and 5-0 arterial silk distally. The freeze-dried homografts were usually smaller in diameter than the proximal host aorta. This proved troublesome on many occasions and required placement of sutures

to compensate for this discrepancy in performing the proximal anastomoses (Fig. 1). After the completion of the proximal and one distal anastomosis, blood was allowed to flow through the homograft to one lower extremity while the opposite iliac anastomosis was being completed. A bilateral lumbar sympathectomy was performed in 16 of the 40 patients.

Massive blood replacement up to 6,000 c.c. was required in management of patients with ruptured aneurysms. For the average elective resection, 1,000 to 2,000 c.c. of blood was usually administered. There were no deaths in the operating room.

Operative Complications.—In 11 patients the inferior vena cava was inadvertently injured during the course of dissecting the aneurysm from this structure. Rents in the vena cava were closed with 4-0 arterial silk. In one instance laceration of an anomalous (retroaortic) left renal vein necessitated the replacement of the left renal vein by a graft. There was one instance of cardiac arrest when an aneurysm ruptured just prior to proximal aortic occlusion. Cardiac massage was successful in restoring a normal sinus rhythm, the aneurysm was resected, and the patient made an uneventful recovery.

Fig. 1.—Freeze-dried homograft sutured in place to restore aortic continuity following resection of the aneurysm. Note discrepancy in diameter of homograft and host aorta.

Pathology.—The aneurysm was found to be atherosclerotic in nature in all 40 cases. No gross or histologic evidence of luetic aneurysm was found. All aneurysms contained laminated thrombus. Liquefaction necrosis within the peripheral layers of the thrombus and the aortic wall was repeatedly encountered (Fig. 2). The phenomenon is considered an important factor contributing to eventual rupture of an aneurysm. The posterior and lateral walls of an aneurysm were found to be the common site of rupture in this study. Degeneration of all layers of the aortic wall, with atherosclerotic and calcium deposits, were the characteristic microscopic changes found in the wall of the aneurysms.

Immediate Results.—An excellent immediate result was obtained by 26 patients who were able to return to a full and active life. Six other patients obtained a good result but were restricted by other disease processes. Table I summarizes the immediate results. There were 8 hospital deaths. Four of the deaths occurred in patients who presented with a ruptured aneurysm. In the nonruptured group the mortality rate was 12.5 per cent. In the last 20 cases of nonruptured aneurysm there was one death.

TABLE I. IMMEDIATE RESULTS OF TREATMENT

STATUS OF ANEURYSM	NUMBER OF PATIENTS	DIED	MORTALITY RATE
Ruptured aneurysm	8	4	50%
Nonruptured aneurysm	32	4	12.5%

Fig. 2.—Cross section of arteriosclerotic aneurysm of abdominal aorta showing laminated thrombus and liquefaction necrosis in peripheral layers.

Table II summarizes the circumstances surrounding the 8 hospital deaths. Rupture of the homograft occurred in one patient who presented with an abscess in the hematoma of a self-limited rupture of an aneurysm. Bacterial infection caused partial dissolution of the homograft with hemorrhage 6 days after operation. The homograft was successfully removed and another implanted; however, the patient succumbed to an overwhelming septicemia 23 days later. At autopsy the second homograft was found to be intact and functioning well.

Postoperative hemorrhage occurred in an 81-year-old patient who had presented with a ruptured aneurysm. Postmortem examination revealed a rent in a tributary of the left renal vein, presumably due to operative trauma. A third death was due to generalized peritonitis secondary to acute appendicitis in a patient who had successfully recovered from renal shutdown. Death due to

TABLE II. ANALYSIS OF DEATHS

CASE	AGE	BLOOD PRESSURE	RUPTURED ANEURYSM	COMPLICATING DISEASE	DEATH POST-SURGERY	CAUSE OF DEATH
1	66	120/64	No	Severe emphysema	10 days	Bronchopneumonia
2	81	180/110	Yes		10 hours	Postoperative hemorrhage
3	68	120/80	Yes	Previous myocardial infarcts	29 days	Rupture of homograft, septicemia
4	63	130/100	No	3 previous myocardial infarcts	4 days	Myocardial infarction
5	67	150/110	Yes	Previous dissecting thoracic aneurysm	38 days	Acute appendicitis with generalized peritonitis
6	72	160/100			5 days	Acute renal necrosis and renal shutdown
7	63	170/110	Yes	Disseminated lupus erythematosus	8 days	Renal shutdown
8	58	230/120	No	Angina pectoris	10 days	Dissecting thoracic aneurysm

acute suppurative bronchopneumonia occurred 10 days after operation in another patient with severe emphysema and bronchitis in spite of tracheostomy and vigorous antibiotic therapy.

Renal shutdown is listed as the cause of death in 2 patients; however, these deaths occurred only 5 and 8 days after operation. Postmortem examination failed to reveal any other cause of death in these patients. Massive myocardial infarction and dissecting thoracic aneurysm rupturing into the pericardium accounted for death in 2 other patients.

In addition, there were 7 patients who had nonfatal complications in the immediate postoperative period. Two patients experienced renal shutdown from which they made a complete recovery. In addition, there were two cases of bronchopneumonia, two instances of thrombophlebitis, and one patient who developed gangrene of the leg which required amputation. Excluding the 5 cases of renal shutdown, a rise in the serum nonprotein nitrogen in excess of 45 mg. per cent was sustained by 25 of the remaining 35 patients.

FOLLOW-UP STUDIES

All patients have been followed from 1 to 4 years and the current status of each has been recently assessed. There have been 5 late deaths which were unrelated to the abdominal aneurysm or its treatment (Table III.) During the interim period between operation for aneurysm and death from unrelated cause (4 to 20 months), there was satisfactory function of the graft in each instance. Postmortem examination was performed in 4 of these patients. Gross and

TABLE III. LATE DEATHS

CASE	AGE	CAUSE OF DEATH	MONTHS POSTOPERATIVE
1	64	Gastrointestinal hemorrhage (duodenal ulcer + cirrhosis)	8
2	64	Congestive heart failure	20
3	62	Myocardial infarction	3
4	61	Respiratory failure, senile emphysema	6
5	67	Cerebrovascular accident	4

microscopic examination of the grafted aorta revealed a patent, functioning graft in each case with no evidence of aneurysmal change, thrombosis, infection, or cicatricial stenosis at suture lines (Fig. 3).

Of the 27 survivors, 26 have been able to return to a full and active life and have been completely relieved of the symptoms of their disease. In all instances, except one, these elderly people have enjoyed good general health and the unrestricted activity of their age group. One patient who obtained an excellent result from his operative procedure has been subsequently partially disabled by a cerebrovascular accident which occurred 6 months after operation.

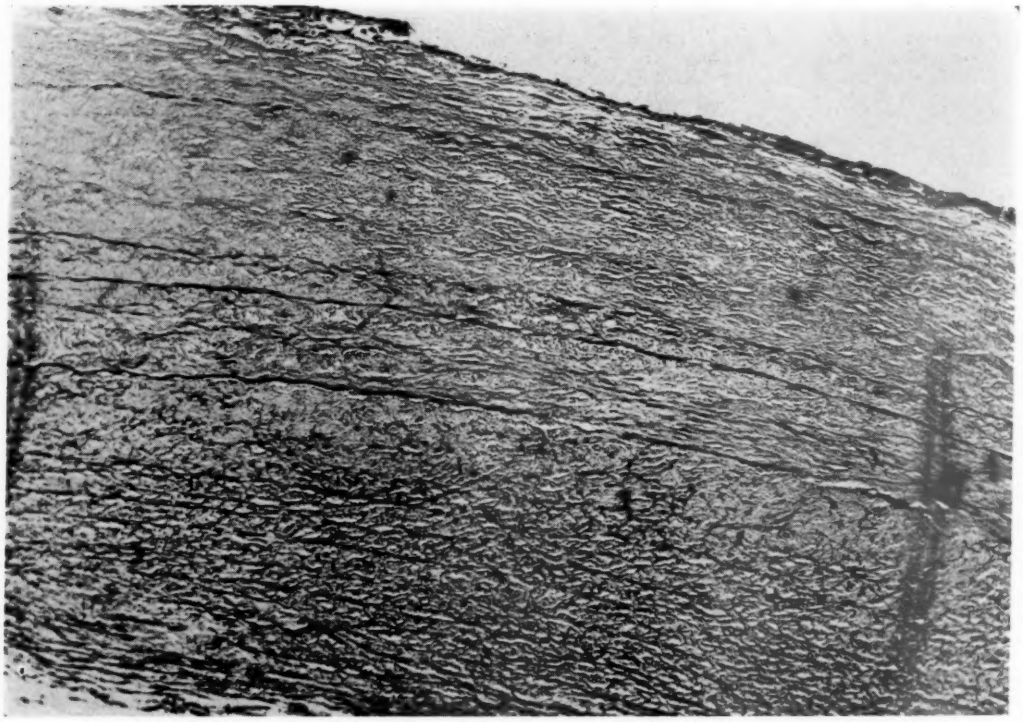

Fig. 3.—Photomicrograph of freeze-dry homograft in a patient who died 8 months after graft implantation. Homograft had been stored for 9 months prior to use. Elastic tissue stain demonstrates persistent elastic layers in homograft.

Postoperative aortograms were carried out in 6 of the patients at periods ranging from 3 months to 3 years after aortic resection. Patent, functioning grafts without stenosis or aneurysmal change were uniformly demonstrated. Current clinical evaluation of all survivors reveals the circulatory status of the lower extremities to be satisfactory with no evidence of recurrent aneurysm or graft failure. In one patient resection of the left colon for diverticulitis was carried out a year after aortic resection. At the time of the second procedure, inspection and palpation of the graft disclosed that it resembled normal aorta in every detail. In the patient mentioned above whose left renal vein was replaced by a homograft at the time of aortic resection there have been no disturbances of renal function as demonstrated by intravenous pyelography in the 2 years since operation.

COMMENT

In recent years the trend in the use of vascular substitutes is toward synthetic plastic prostheses and away from homografts. Currently available prostheses have many characteristics which seem to indicate that this trend is logical and desirable.[7, 8, 15] The behavior of synthetic prostheses as vascular substitutes over a long-range period is a matter of great interest, but thus far observations are necessarily limited.[7] It seems desirable to record available data concerning the performance of homografts over prolonged periods in order to establish standards with which the behavior of synthetic materials can be compared in the future.

This study indicates that freeze-dried homografts have performed well as aortic substitutes following resection of abdominal aortic aneurysm. Thus far, observations up to 4 years in duration indicate satisfactory function without evidence of aneurysmal dilatation or thrombosis. There have been no late deaths attributable to failure of the graft. The surviving patients have been restored to a normal and active life. As DeBakey[9] has pointed out, the life expectancy of such patients has been increased. Table IV tabulates the number of patients operated upon in each year of the study as well as the survivors for each year. Estes[11] tabulated the survival figures in 102 untreated abdominal aortic aneurysms, in similar age groups, and found that 26 per cent survived 4 years from the time of initial symptoms. The follow-up figures in Table IV date from the time of resection of the aneurysm and indicate a threefold increase in survival as compared to the data presented by Estes. Blakemore[4] has recorded similar figures for patients treated some years ago by wrapping, wiring, banding, and so forth. Once again, dating from initial symptoms, Blakemore found 50 per cent of the patients survived 2 years and 30 per cent survived 4 years. Although the number of patients involved in the present study is small, the 2, 3, and 4-year survival figures far exceed those reported by Estes and Blakemore and are similar to the large series reported by DeBakey and his associates.[9]

TABLE IV. SURVIVAL RESULTS

	PATIENTS ENTERING STUDY EACH YEAR			
	APRIL, 1954-JUNE, 1955	JULY, 1955-JUNE, 1956	JULY, 1956-JUNE, 1957	TOTAL
Number of patients	16	12	12	40
Survivors, July, 1958*	11	8	8	27
Percentage surviving	69	67	67	68

*Nonsurvivors include hospital and late deaths.

It is obvious that in treating patients with arteriosclerotic aneurysm of the abdominal aorta, most of whom are elderly, many will have other serious diseases. That such patients can undergo resection of abdominal aneurysm with a low mortality rate is indicated by the last 20 patients of this series and the reports of other clinics.[3, 7, 9, 13] It has been repeatedly observed that as experience with resection and grafting accumulates, the operative mortality rate falls progressively. This would seem to indicate that coexisting and complicating diseases are of less importance than the skill and experience of the surgical team. Rupture of an abdominal aneurysm prior to surgical intervention has been the

greatest deterrent to a successful outcome. Eight patients in this series presented this picture and four of them died. Two of these patients had been known to have an aneurysm for 15 to 36 months, respectively. Prompt surgical intervention in patients with known or suspected aneurysm is obviously strongly indicated.

The high incidence of renal complications in the present series is noteworthy. The rather consistent rise in the postoperative serum nonprotein nitrogen probably reflects a renal vasoconstrictive response to temporary aortic occlusion. The use of sympathetic blocking agents such as Arfonad during aortic occlusion has proved helpful. Its use in the last 5 patients of this series was accompanied by a normal postoperative serum nonprotein nitrogen level and excellent urinary output.

While this study indicates that freeze-dried homografts are excellent aortic substitutes, they have certain disadvantages. Available sources of supply of homografts are limited. Maintenance of exacting standards in the processing and preservation of homografts is constantly required. The freeze-dried homograft is frequently of insufficient diameter for proper anastomosis to the host aorta in patients with aneurysmal disease. For these reasons, the synthetic prostheses have largely replaced homografts in recent years. However, prolonged observation of the behavior of both homografts and synthetic prostheses as aortic substitutes will be required before a conclusive evaluation can be made.

SUMMARY

A follow-up study of freeze-dried homografts in the treatment of patients with arteriosclerotic aneurysm of the abdominal aorta has been conducted. Observations of 1 to 4 years in duration indicate satisfactory function of these arterial substitutes. There have been no instances of aneurysmal dilatation or thrombosis of the homograft.

In a group of 40 patients with abdominal aortic aneurysm treated over a 3-year period, there were 8 hospital deaths. Four of the deaths occurred in patients with rupture of the aneurysm prior to surgical intervention. There was one death in the last 20 patients.

The surviving patients have been restored to a full and active life. Survival data indicate that the life expectancy of these patients has been increased.

The follow-up observation on the behavior of freeze-dried homografts which has been presented provides data with which the synthetic prostheses, now being used, can be compared in the future.

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ILIAC ARTERIOGRAPHY IN CONJUNCTION WITH LUMBAR SYMPATHECTOMY IN PERIPHERAL VASCULAR DISEASE

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INTRODUCTION

THE rapid advances in vascular surgery during the last decade have made necessary a re-evaluation of lumbar sympathectomy in the treatment of peripheral vascular disease of the lower extremities. In an attempt to correlate the results of sympathectomy with the anatomic site of vascular involvement and to compare these results with direct or replacement procedures in which grafts are employed, we have instituted common iliac arteriography as a routine procedure at the time of lumbar sympathectomy. This study was instituted in 1957, and to date over 50 such procedures have been performed without morbidity or mortality attributable to the arteriography.

This report includes 42 men upon whom 51 lumbar sympathectomies and common iliac arteriograms or aortograms were performed from February, 1957, to July, 1958. In 3 patients upon whom left lumbar sympathectomies were performed, distal aortograms were obtained. In the remaining 39 cases, iliac arteriograms were performed.

The patients ranged in age from 30 to 72 years. The greatest number were in the 61 to 70 years age group, which accounted for 27 cases or 64 per cent (Table I).

Table I. Diseases and Age Incidence

Clinical Diagnoses	Number of Cases	Age						Per Cent of Total
		21-30	31-40	41-50	51-60	61-70	71-80	
Arteriosclerosis obliterans	22	–	–	–	5	16	1	52.4
Diabetic gangrene	9	–	–	1	1	7	–	21.4
Embolism/thrombosis	3	–	–	–	–	3	–	7.1
Chronic thrombophlebitis	4	1	–	–	2	1	–	9.5
Frostbite	2	–	1	1	–	–	–	4.8
Causalgia	2	–	2	–	–	–	–	4.8
Totals	42	1	3	2	8	27	1	100.0

The cases were divided into the following categories: arteriosclerosis obliterans, diabetic gangrene or impending gangrene, arterial embolus or acute thrombosis, chronic thrombophlebitis with stasis ulceration, frostbite, and causalgia.

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Arteriosclerosis obliterans accounted for the largest number of patients representing 22 cases or 52.4 per cent of the total. If diabetic gangrene or impending gangrene is added to this group, it totals 31 cases or 83.7 per cent. Chronic thrombophlebitis with stasis ulceration accounted for 4 cases or 9.5 per cent while arterial embolism or thrombosis occurred in 3 cases or 7.1 per cent. Frostbite and causalgia each accounted for 2 cases or 4.8 per cent of the total (Table II).

TABLE II

CLINICAL DIAGNOSES	NUMBER OF CASES	PERIPHERAL PULSES ABSENT OR DIMINISHED	PAIN	ULCERATION	EDEMA	NUMBNESS	CELLULITIS	GANGRENE OR IMPENDING GANGRENE
Arteriosclerosis obliterans	22	21	21	3	1	2	2	3
Diabetic gangrene	9	7	2	4	0	2	0	9
Embolism/thrombosis	3	3	3	0	0	3	0	0
Chronic thrombophlebitis	4	0	3	4	2	0	1	0
Frostbite	2	0	2	0	0	1	0	0
Causalgia	2	0	2	0	0	0	0	0
Totals	42	31	33	11	3	8	3	12

SURGICAL TECHNIQUE

Spinal anesthesia was used in almost all cases. Following administration of the anesthetic, the patient is placed on the improvised cassette holder in the supine position (Fig. 1). As the surgery is begun, the anesthetist administers a 1 c.c. test dose of 50 per cent Hypaque intravenously. If there are any side effects from the dye, arteriography is omitted. Lumbar sympathectomy and iliac arteriography (or aortography) were performed through a transverse abdominal muscle-splitting incision placed at the level of the umbilicus.[1] The lumbar sympathetic chain is exposed by the extraperitoneal route and is excised from the level of the second lumbar vertebra to the sacral promontory, which usually includes the second, third, and fourth lumbar sympathetic ganglia. The common iliac artery is then exposed and palpated. An area devoid of atheromatous or arteriosclerotic plaques is then selected and penetrated with a slightly curved 2-inch 20-gauge needle and 10 c.c. of 50 per cent Hypaque is injected at moderate speed (25 c.c. is used for aortography). An exposure is then made using an ordinary portable x-ray unit (Fig. 2) synchronized with the beginning of the injection. Depending upon the size of the patient, the exposure is made from 2 to 4 seconds at 80 to 90 kilovolts and 20 milliamperes, with the tube focused on the mid-thigh area. The cassette holder was made by our engineering department from one-half inch plywood and lead shielding (Fig. 3). It holds two conventional 14 by 17 inch cassettes, half of each of which is exposed at a time allowing two full-length exposures to be made of the extremity. The second exposure is made as rapidly as the cassettes can be pushed over in the holder, which usually is during the time when the injection is just being completed.

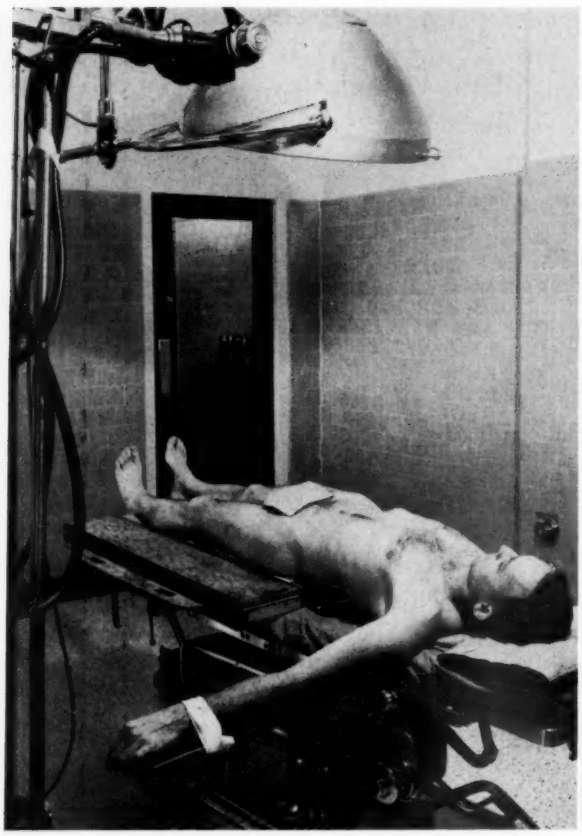


Fig. 1.

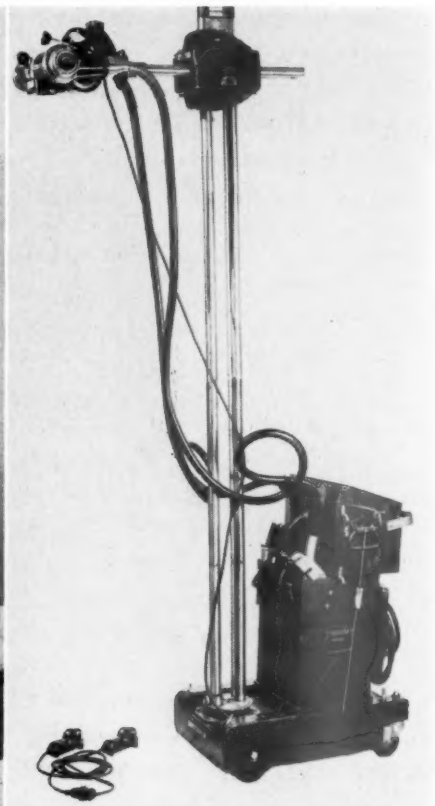


Fig. 2.

Fig. 1.—Patient and equipment in position for radiographic exposure.
Fig. 2.—Portable x-ray unit.

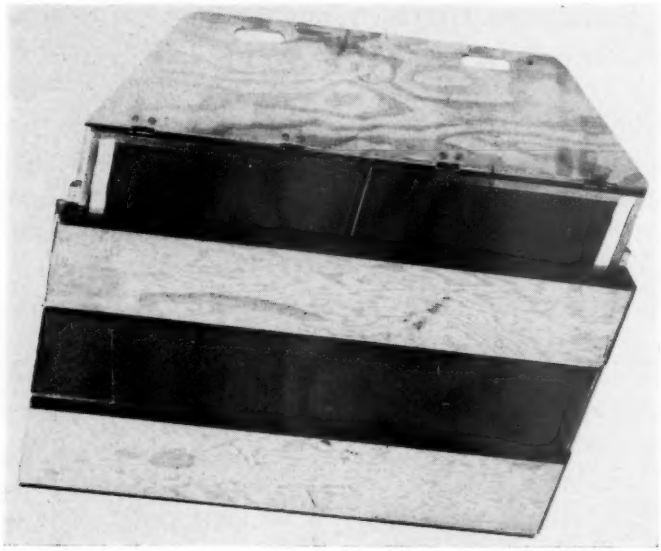


Fig. 3.—Cassette holder with cassettes in place for first exposure. The cassettes are pushed in for the second exposure.

In the 42 patients reported upon here, 51 arteriograms were performed, the vast majority of which were done by the resident staff. Of the 51 attempted, 14 were failures, nearly all of which occurred early in the series when we were attempting to standardize our technique. We encountered many technical difficulties, some of which included (1) failure to make the injection under direct vision resulting in the needle slipping out of the vessel or through the back wall of the vessel resulting in a pool of dye; (2) poor timing due to very rapid injection of the dye with faster x-ray exposures; and (3) not starting the exposure until almost all of the dye had been injected. On the other hand, certain early refinements such as suturing on of skin towels and the use of Lucite Deaver retractors have been dispensed with as they were not in the x-ray field and did not interfere with visualization of the arterial tree.

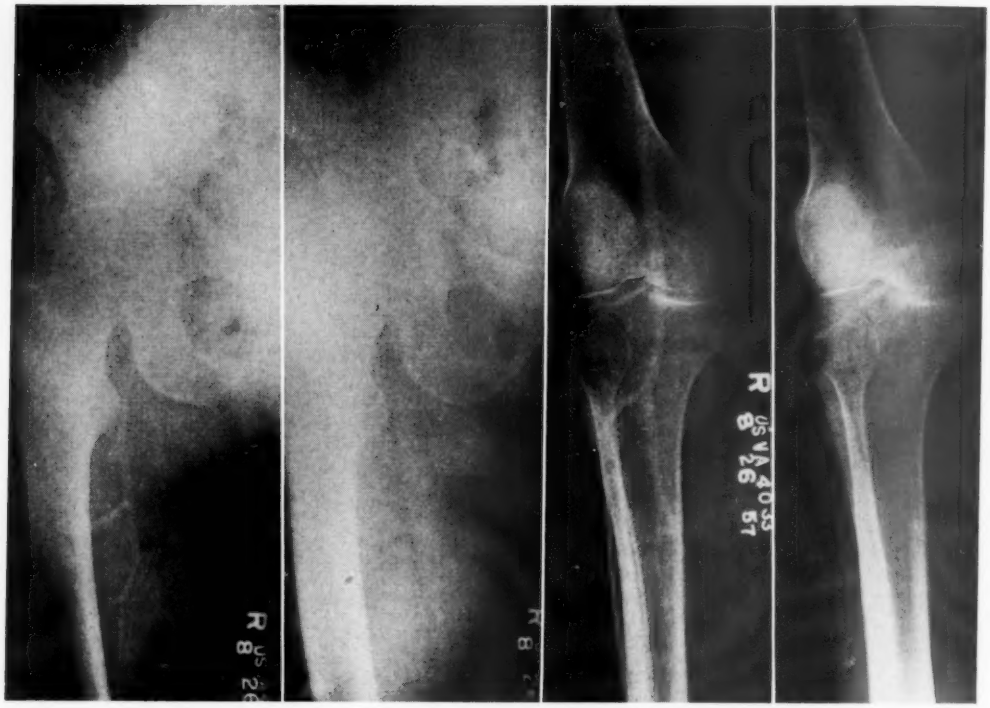
Following completing of the arteriogram the wound is inspected for bleeding and then closed in the majority of cases by the "nonsuture" technique described elsewhere[3] in which only the external oblique aponeurosis, subcutaneous tissue, and skin are approximated with fine silk sutures. A light dressing is then applied, which is removed later in the day on ward rounds, or the next morning.[2] If there is no visualization on the arteriograms, no attempt is made to repeat the arteriogram. The patient is ambulated the same evening or the following morning unless gangrene is present.

FINDINGS

Of the attempted 51 arteriograms, 14 were failures. The findings in the 37 successful arteriograms were as shown in Table III. The totals listed exceed the number of successful arteriograms because of bilateral findings on aortography. There appeared to be little significant correlation between the arteriographic findings and the severity of the clinical disease, since amputations were required in 2 cases with "normal" arteriograms and in one case with diffuse arteriosclerotic changes. The most common site of obstruction was at the origin of the superficial femoral artery. Only one of these patients required amputation. In this series there were 3 deaths. One patient had chronic uremia and died from that cause several days following surgery. The second patient died of aortic thrombosis following an unsuccessful thromboendarterectomy of a thrombus high in the common iliac artery. The third patient died of congestive heart failure on the first postoperative day. In this case sympathectomy was performed for a popliteal embolism, and later in the day of surgery, he again developed embolic occlusion of the femoral artery and went into profound shock. His status was too grave to warrant

TABLE III

Normal visualization	14 (Fig. 4, *A* and *B*)
Superficial femoral obstruction	13 (Fig. 5, *A* and *B*)
Common femoral obstruction	2 (Fig. 6, *A* and *B*)
External iliac obstruction	1 (Fig. 7, *A* and *B*, 8, *A* and *B*)
Deep femoral obstruction	1
Diffuse arteriosclerosis	8 (Fig. 9, *A* and *B*)



A. *B.*

Fig. 4.—*A*, "Normal" arterial tree. *B*, "Normal" arterial tree.

A. *B.*

Fig. 5.—*A*, Superficial femoral artery obstruction at its origin. Deep femoral fills well. *B*, Note filling of the distal arterial tree via collateral circulation.

A. *B.*

Fig. 6.—*A*, Common femoral artery obstruction. *B*, Note delayed filling of distal superficial femoral artery by collateral circulation.

A. *B.*

Fig. 7.—*A*, External iliac artery obstruction extending into common femoral artery measuring 11.5 cm. The deep femoral artery is not visible. *B*, Superficial femoral, popliteal, anterior, and posterior tibial arteries well visualized.

Fig. 8.

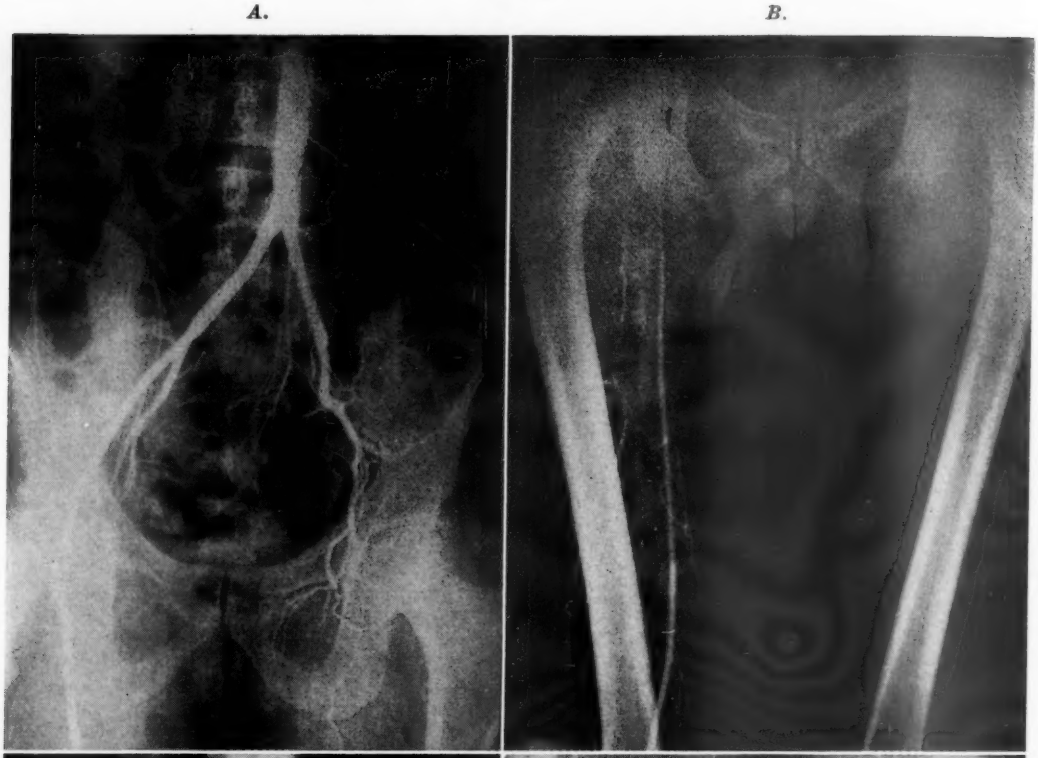


Fig. 9.

Fig. 8.—*A*, Aortogram revealing obstruction of external iliac artery at its origin. This film is included for its excellence but is not part of the present series. *B*, Failure of superficial or deep femoral arteries to fill below the obstruction.

Fig. 9.—*A*, Diffuse arteriosclerotic changes on distal aortogram. *B*, Note marked irregularity of the dye column in the left superficial femoral artery, and failure of middle segment to fill on the right.

embolectomy, and therefore intravenous heparin was given. This resulted in a large retroperitoneal hematoma and blood was cautiously given the following day. He rallied from the shock but died of congestive heart failure in the evening of the first postoperative day.

SUMMARY

A technique for common iliac arteriography is described. To date over 50 such procedures have been carried out without incident due to the arteriography. While this series is too small to draw definite conclusions, it is being continued in the attempt to correlate the symptoms and physical findings with the anatomic site of obstruction as determined by arteriography and to evaluate the results of lumbar sympathectomy in their treatment. We feel this method of arteriography is a valuable method in determining the status and patency of the arterial tree and should allow the comparison of the results of lumbar sympathectomy and direct arterial surgery for similar types of obstruction and determine their relative merit. We plan to publish these results in the future when more definite conclusions can be drawn.

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FROZEN SECTIONS

An Evaluation of 1,810 Cases

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THE use of frozen sections for prompt diagnosis of surgical specimens has been established as an accepted procedure in hospitals throughout the country. This method of diagnosis has become almost indispensable in the surgical management of breast tumors and other lesions of questionable nature. Properly employed, this means of establishing a diagnosis enables the surgeon to proceed with immediate definitive therapy when indicated. Furthermore it spares the patient additional anesthesia, operating room fees, and the anxiety associated with waiting for a diagnosis.

Pathologists are now expected to be capable of rendering frozen section diagnoses on tissue from any part of the body with reasonable accuracy. What constitutes reasonable accuracy was not delineated until Jennings and Landers[2] and Fuller[1] published data to show their results in specific organs.

A similar study has been carried out to determine the accuracy of frozen sections at the Garfield Memorial Hospital (now the Washington Hospital Center). It was started on July 7, 1953, and included every case submitted through Sept. 19, 1958. The frozen sections were prepared and interpreted by all members of the Department of Pathology and some of the residents in pathology. The diagnoses were recorded immediately and the final diagnoses based on paraffin sections were entered the next day.

MATERIAL

A total of 1,810 specimens from virtually every organ of the body were frozen during the period of this study. The number of cases, the errors, and the percentage of accurate diagnoses are shown in Table I. The accuracy for the entire series was 97.6 per cent. In the majority of cases it was possible to make a correct diagnosis on the specimen submitted, but a total of 43 errors were made. In 22 of these the inability of the pathologist to make a precise diagnosis resulted in the postponement of further surgery. In calculating the accuracy of the method the cases of inconclusive diagnoses were counted as errors because they were regarded as failure of the technique to yield an immediate diagnosis, the ultimate purpose of the method.

There were 18 false-negative reports, most of which occurred in breast tissues. Three false-positive diagnoses were made. A leukoplakia of the vulva was reported as in situ carcinoma, a pseudomucinous cystadenoma of the ovary

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was thought to be carcinoma, and a lymph node from a patient with cat scratch disease was mistaken for lymphosarcoma. Fortunately no extensive surgery was performed as a result of these errors.

In Table I are listed the results obtained in the organs most frequently frozen and certain other tissues often considered to be difficult to handle.

TABLE I

TISSUE	TOTAL FROZEN SECTIONS	ERRORS	ACCURACY (PER CENT)
Breast	1,004	19	98.1
Thyroid	231	8	96.5
Lymph node	122	7	94.3
Lung	57	0	100.0
Skin	42	1	97.6
Intestinal polyp	37	0	100.0
Salivary gland	23	1	95.7
Prostate	22	1	95.4
Pancreas	15	0	100.0
Brain	14	0	100.0
Endometrium	12	0	100.0
Miscellaneous	231	6	97.4
Total	1,810	43	97.6

During this study, 1,083 breast operations were performed. In certain cases of gynecomastia, chronic cystic mastopathy, and typical fibroadenomas, the surgeon and the pathologist agreed after examination of the gross specimen that the lesion was benign and that a frozen section was not required. No errors have been made as a result of this type of examination. There were 278 malignant breast lesions including 2 cases of cystosarcoma phyllodes. In 49 of these the diagnosis was established either by aspiration biopsy or, where there was advanced disease, by conventional biopsy.

Frozen sections were done on 1,004 biopsy specimens, 229 of which were malignant. Eight were erroneously reported as benign and 11 as uncertain. There were no false-positive reports. Thus 98.1 per cent of all breast biopsies frozen were correctly diagnosed. Mistakes were most common in the rare or unusual cancers. They included 5 infiltrating lobular carcinomas, 3 papillary carcinomas, 3 in situ carcinomas, and 2 colloid carcinomas. Changes associated with pregnancy have on occasions caused considerable confusion because of the extreme lobular proliferation.

Surgeons have often expressed doubt about the reliability of frozen section diagnoses on thyroid glands. One notable exception was Lahey[3] who stated that Meissner maintains a 95 per cent accuracy. Undoubtedly other institutions have an equally satisfactory record. During the present study 718 thyroid glands were surgically removed. A frozen section diagnosis was requested in 231 cases. Included were 28 per cent of the nontoxic nodular goiters, 42 per cent of the glands showing "chronic thyroiditis," 48 per cent of the adenomas, and 64 per cent of the carcinomas.

Forty-one patients with thyroid carcinoma were treated surgically during this period. The diagnosis of advanced undifferentiated carcinoma was established by aspiration biopsy in 2 patients. Only 25 of the remaining 39 primary

thyroid cancers were frozen. Lack of confidence in frozen sections probably led some surgeons to be content to wait 24 hours for the paraffin section diagnosis. In other cases it seems probable that carcinoma was not recognized grossly.

Of the 231 thyroid glands submitted for frozen section a correct diagnosis was made in 223 cases or 96.5 per cent. The errors include 7 false-negative reports and one which was called uncertain. There have been no false-positive diagnoses. Six of the cases misdiagnosed were papillary and follicular carcinoma and two were undifferentiated carcinoma. Review of these cases showed that four were difficult to diagnose even with good paraffin sections.

The poorest results were obtained in lymph nodes. In addition to the cat scratch disease which was reported as lymphosarcoma, we failed to recognize Hodgkin's disease in one node and reticulum cell sarcoma in another. Metastatic carcinoma was not seen in the frozen section of 4 nodes but appeared as small foci in the paraffin sections. Review of the frozen sections revealed a focus of carcinoma which had been missed in one node. This observation coroborates the work of Saphir and Amromin[4] who found that single sections of axillary lymph nodes from radical breast operations revealed only 66 per cent of the foci of metastatic carcinoma present in the nodes. It also shows the fallacy of determining the extent of an operative procedure by the results of frozen sections on single or even several nodes.

Prior to reading the paper by Jennings and Landers, we had declined to freeze endometrial curettings. Since that time 12 endometrial specimens have been examined by frozen section without error. Three of these were adenocarcinoma. The cases not specifically listed in the table were included in the miscellaneous category. Most of these were specimens from various sites in the abdominal cavity, the liver, the ovaries, and the gastrointestinal tract. Numerous biopsies of the cervix, testes, and mediastinum were also examined. No single organ accounted for more than one error in the miscellaneous group.

DISCUSSION

There are several uses for frozen section at the time of operation, but basically they are indicated only when immediate additional therapeutic procedures are contemplated. In most cases no further surgery will be indicated after the initial biopsy. In others definitive surgery for cancer will follow and in some the frozen section will prove the lesion to be inoperable. Frozen sections are sometimes made to determine if the margins are free of tumor when excising a basal cell carcinoma or other malignant lesions of skin and mucous membranes. They may be indicated to verify a diagnosis of carcinoma in the abdominal or pleural cavity so that a chemotherapeutic agent can be instilled immediately. The procedure may also be used to establish a diagnosis of adenocarcinoma of the endometrium when the immediate use of radium is indicated.

The surgeon and the pathologist must each accept certain responsibilities if the patient is to receive the maximum benefit from the frozen section procedure. The pathologist must be informed as to the exact site of the biopsy and he must have pertinent clinical information such as sex, age, presence of

pregnancy, and history of previous tumors. It is probable that some of the errors in this series could have been avoided if adequate clinical information had been available. The surgeon must obtain a representative and adequate biopsy. Crushing of tissue destroys natural relationships and leads to errors. Careful selection of one biopsy will usually result in a definite diagnosis and will save the patient the time and cost of freezing multiple biopsies. The surgeon should realize that it is the pathologist who must decide whether a given specimen can be frozen and interpreted satisfactorily or whether it would be wiser to wait for the paraffin sections.

It is incumbent upon the pathologist to become proficient in the preparation and interpretation of frozen sections. Adequate amounts of surgical and autopsy material are always available for practice. Pathologists must make themselves available when frozen sections are requested and should report their findings directly to the operating surgeon. Patients with unusual diseases are sometimes benefited by consultations which follow the report. To facilitate this procedure the frozen section room should be incorporated in the operating suite. Finally the pathologist should be cautious and remember that it is better to admit uncertainty than to give a false-positive diagnosis which might result in unnecessary surgery.

Frozen section techniques vary somewhat in different institutions. The most important step in any method is the thorough inspection of the specimen and selection of the most suspicious area for examination. This must always be done by the pathologist or resident. Too much depends on the frozen section diagnosis to allow a technician without adequate knowledge of medicine or gross pathology to perform these tasks. Thin blocks measuring approximately 1 cm.^{2} are most easily frozen. When cut at 12 microns, good sections can be obtained which are easily handled and quickly stained. The tissues are dehydrated with alcohol, stained with hematoxylin and eosin, and mounted in Permount so that they can be kept permanently. This procedure requires an average of 6 minutes from the time the tissue is submitted to the pathologist to the time the diagnosis is made. Considerable care is required to obtain good sections of papillary tumors, polyps of the colon and soft tissues such as colloid carcinomas of the breast, certain ovarian tumors, and thyroids. It has been found helpful to fix these tissues in boiling 10 per cent formaldehyde for 30 seconds before freezing. When microscopic interpretation is difficult, the preparation of slides from 2 or 3 different portions of the specimen sometimes makes a definite diagnosis possible.

Most of the errors were made in the first years of this study. The gradual improvement reflects increasing diagnostic and technical skill, self-confidence, and the examination of several portions of tissue in difficult cases. The clinical information obtained by being present in the operating room accounts in part for the reduction of errors.

SUMMARY

An analysis of 1,810 frozen sections is presented to show their accuracy in specific organs.

The accuracy attained for the entire series was 97.6 per cent. For specific organs the accuracy varied between 94.3 per cent for lymph nodes and 100 per cent for other organs. For breasts and thyroids, the tissues most frequently examined, the accuracy was 98.1 per cent and 96.5 per cent, respectively.

The indications for frozen sections and their limitations are outlined, and the responsibilities of the surgeon and the pathologist are discussed.

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A SIMPLE OPERATING ROOM ELECTROCARDIOGRAM MONITOR

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THE utility of continuous monitoring of a patient's electrocardiograph during anesthesia and surgical operations is well documented. Many surgeons and anesthetists are prevented from using this aid by the expense involved in acquiring apparatus approved for use in operating rooms. Described here is a transistorized preamplifier, easily constructed, and designed to produce an impulse that may be viewed on a standard oscilloscope.

The circuit is a balanced, grounded emitter, transistor amplifier. Individual base-bias control is provided by one megohm potentiometers in the base circuit. Gain balance is accomplished by the 100 K ohm potentiometers in the collector circuit. Provision is made for the equivalent of a one millivolt test signal obtained and adjusted through the 5 megohm potentiometer. The only controls on the panel are the vertical position adjustment consisting of a 100 K ohm potentiometer, the test signal button, and the on-off switch.

The above portion of the circuit diagrammed, connected to a medium gain, direct coupled, balanced input oscilloscope permits one to view the ECG. The simple version has been expanded to provide write-through from the patient cable to a standard ECG recorder whose impulse is also displayed on the oscilloscope. An R.F. choke filter may be incorporated in each side of the circuit, as shown, to minimize the danger of burned out transistors from electrocautery. The patient cable is best used with needle electrodes rather than standard plate electrodes because of the circuit's low input impedance. The remote possibility that a fault in the oscilloscope might direct its accelerating voltage to the patient can be obviated as shown, by four 390 K ohm 2 watt current-limiting resistors.

Circuit adjustment follows: The 100 K ohm gain balance is centered and collector-to-ground voltage as measured by a high-resistance voltimeter adjusted to approximately –7V with the one megohm bias controls. Transistor gain either side of ground is equalized by the 100 K ohm potentiometer in the collector circuit which serves as a hum balance control. If the write-through feature is not employed, the one millivolt test signal may be adjusted to equal that portion of the QRS impulse observed on a standard ECG and compared to its standardizing signal.

If the write-through switch is employed, a patient is connected to the preamplifier and the preamplifier-ECG cable is connected to a standard machine.

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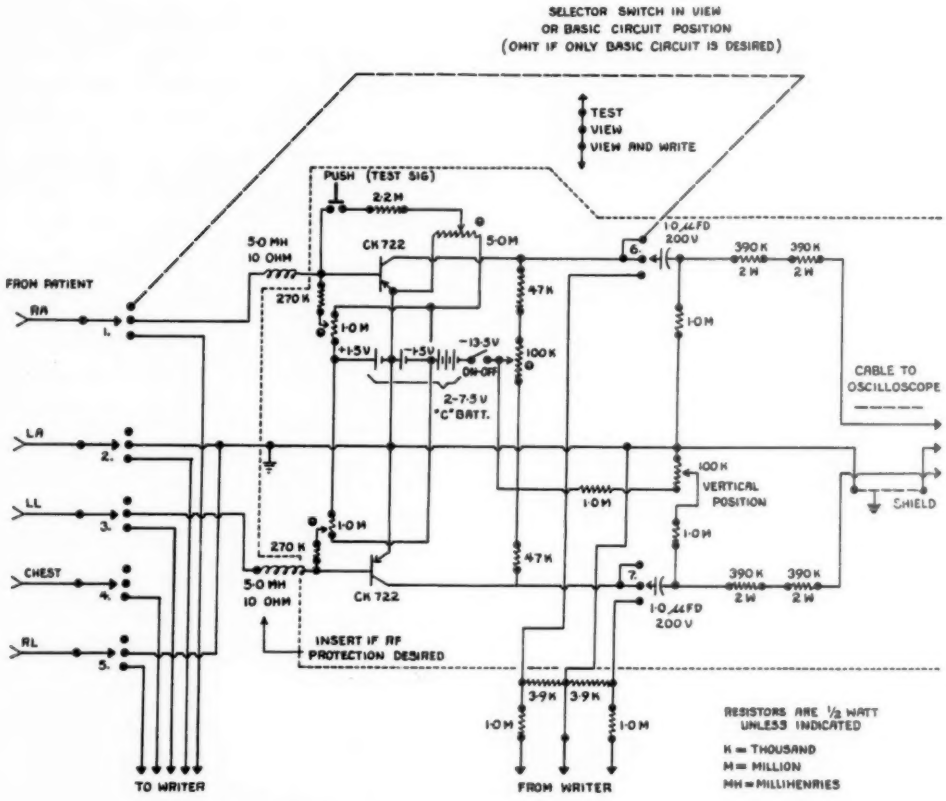

Fig. 1.—Circuit diagram of complete ECG preamplifier.

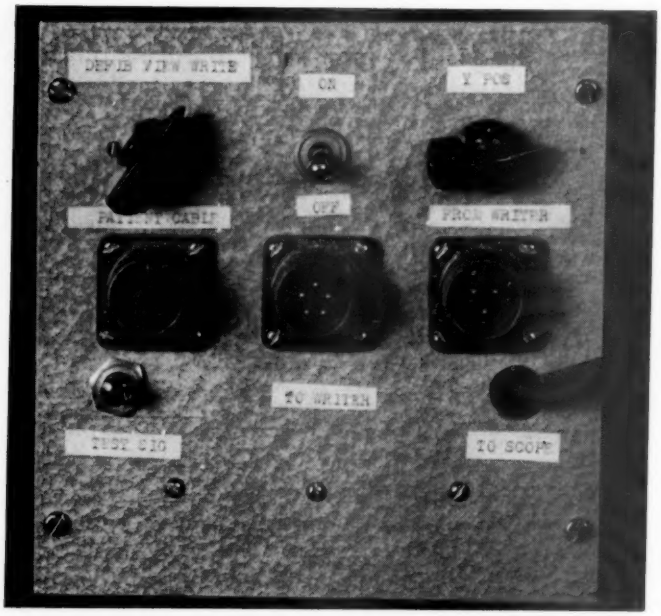

Fig. 2.—Photograph of preamplifier.

With the selector switch in the View and Write position the height of the standard signal is compared to the height of the patient's QRS. The preamplifier test signal is then adjusted to a comparable portion of the QRS produced through the preamplifier by switching from View to Test and back. Some may desire to eliminate the 1 MV signal altogether.

The oscilloscope can be mounted in the wall above 5 feet to conform to N.F.P.A. requirements. The preamplifier operates on 15 V which is above N.F.P.A. limits and may be similarly mounted. However, the current drain is very small, and the mounting box may be strong and might easily be sealed by those who do not care to take the negligible risk of using the device in explosive atmospheres.

A CASE OF NEUROFIBROMA OF THE INTRATHORACIC VAGUS NERVE IN A WOMAN WITH RECKLINGHAUSEN'S DISEASE

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RECENTLY we have had occasion to resect a neurofibroma of the intrathoracic vagus nerve in a woman who suffered from von Recklinghausen's disease. It appeared to us that this case was worth publishing not only because this condition is quite rare, but also because the radiographs made by the radiologist of our hospital in the course of their investigation were of such pronounced diagnostic interest. As far as we have been able to find, the international literature contains descriptions of only 6 such cases. These were reported by Blades and Dugan,[1] Efskind and Liavaag,[3] Gerbode and Marguiles,[6] Gilbertsen and Lillehei,[7] Tuttle, Sanai, and Harms,[8] and Davis and Brown.[2] Furthermore Furrer and Fox,[5] in 1950, have observed a case of fibrosarcoma of the vagus nerve at autopsy.

The case described by Gerbode and Marguiles occurred, just as our case, in a patient with von Recklinghausen's disease. In the case described by Gilbertsen and Lillehei, the condition was bilateral and also involved both recurrent nerves, so that ablation of the tumor caused interruption of the recurrent nerve on the left side, while on the right the resection could not be completed, as the nerve had to be spared.

The modifications of arterial pressure and of the pulse rate brought about by the bilateral interruption of the vagus nerves have been studied by Fraser and Chapman.[4] Of all the cases mentioned, only that tumor encountered in a patient at postmortem examination by Furrer and Fox was malignant.

We might add that none of the articles referred to includes a complete radiologic documentation of the condition in question.

CASE REPORT

The patient was a 67-year-old woman from Parma, Italy. In 1925, she had been subjected to an operation for removal of a new growth which had developed in the left supraclavicular fossa. In the course of the operation the surgeon had warned the patient's relatives that complete removal of the tumor would probably have caused paralysis of the left arm. The patient could not describe the exact nature of the tumor, but she remembered that the arm had been paralyzed for a few months, after which normal mobility had returned. About 3 months before we first saw her, the patient noted that her voice was diminishing. Because of this disturbance she had been subjected to clinical examination and to radiologic examination of the chest which revealed the presence of an anomalous mass, the size of a hen's egg, situated in the superior mediastinum.

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Revision for publication by Dr. R. C. Lillehei, Minneapolis, Minn.
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The patient was admitted to our Surgical Department on April 1, 1958. On physical examination the patient was considerably weakened and the voice was muffled. Moreover, she was affected with a diffuse Recklinghausen's neurofibromatosis (Fig. 1). The systolic blood pressure was 140 mm. Hg, the pulse rate 82 per minute, and the ECG was normal.

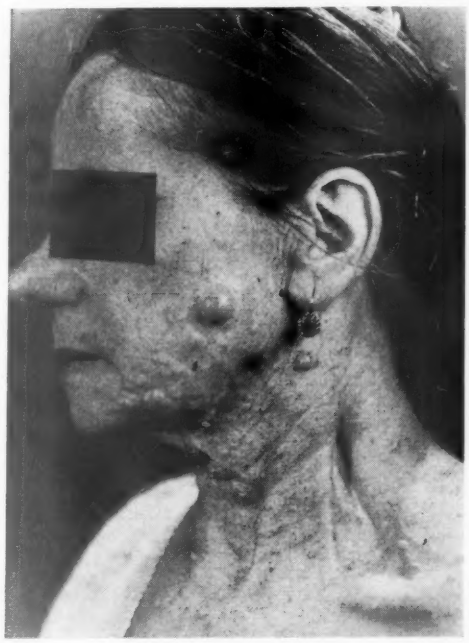

Fig. 1.—A photograph of the patient. The scar of the cervical region is visible.

Fig. 2.

Fig. 3.

Fig. 2.—Radiograph of the chest in the dorsoventral projection.
Fig. 3.—Radiograph of the chest in the right laterolateral projection.

There were no abnormalities of the head. The left supraclavicular fossa showed the scar of the earlier operation which was 7 cm. long and ran parallel with the course of the brachial plexus.

Fig. 4.—Stratigram of the thorax in the lateral projection 1 cm. right of the median plane. The dorsoventral curving of the trachea is distinctly visible.

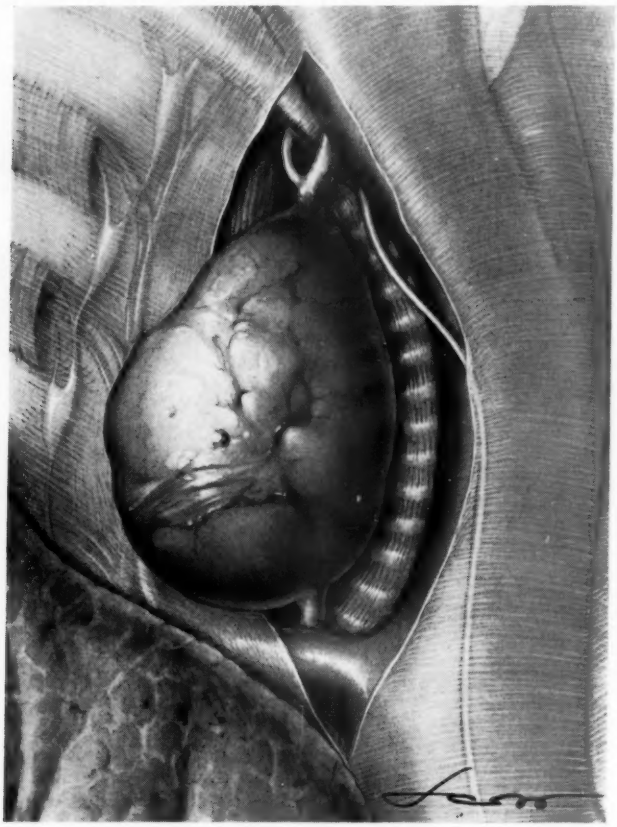

Fig. 5.—The tumor seen at operation.

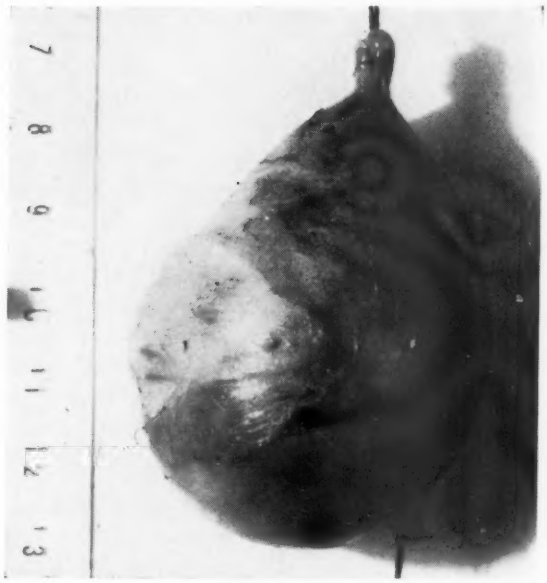

Fig. 6.—The macroscopic aspect of the tumor.

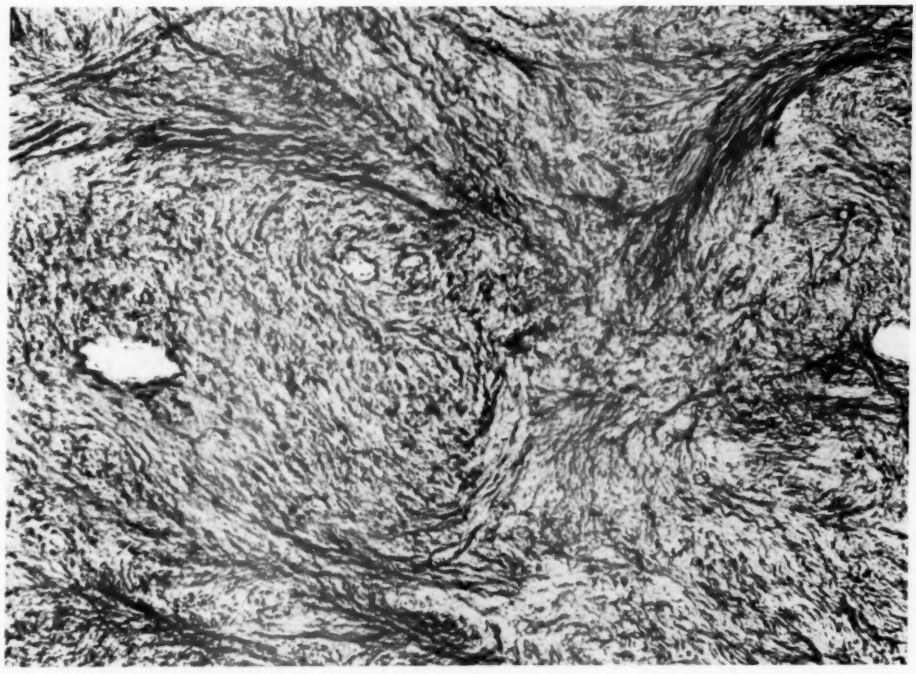

Fig. 7.—The microscopic aspect of the tumor.

In every other respect the objective examination was wholly negative. Radiologic examination of the chest, carried out in two projections and completed with stratigraphy revealed the presence of a rounded mass in the right paratracheal region in the upper mediastinum. This was the size of a hen's egg and had distinct, regular margins (Figs. 2 and 3). The trachea was curved forward and, together with the esophagus, was displaced a little to the left (Fig. 4). No parenchymal alterations nor other abnormalities of the mediastinal shadow could be seen. Indirect laryngoscopy showed paresis of the right vocal cord.

Despite the fact that the posterior mediastinum was not involved, the mass was thought to be a neurofibroma in view of the patient's obvious concomitant neurofibromatosis.

On April 2, 1958, an anterolateral thoracotomy was carried out through the bed of the fourth rib. The tumor was firm, elastic, and oval in shape, and was covered by the mediastinal pleura which adhered to the upper lobe of the lung. It had displaced both the trachea and the superior vena cava anteriorly. After the mediastinal pleura had been opened, the tumor was isolated and found to be connected with the trunk of the right vagus nerve (Fig. 5) which penetrated into it some 5 to 6 mm. below the point where the right recurrent nerve emerges. This nerve was stretched downward to such an extent that it had lost its normal contact with the subclavian artery. Lower down, the vagus nerve emerged again from the tumor mass and, after a few millimeters, disappeared behind the azygos vein. The tumor was removed by dividing the right vagus nerve but sparing the recurrent nerve (Fig. 6). The raw area in the mediastinum was covered with pleura and the thoracotomy wound closed in layers. No change in the cardiac rhythm was noted during the operation. The postoperative course was uneventful and the patient was discharged as cured on May 2, 1958. Histologic examination of the removed specimen revealed a neurofibroma without signs of malignancy (Fig. 7). The patient was seen on a follow-up visit on Aug. 1, 1958, and was in excellent condition. Laryngoscopy at this time showed only slight weakness in the right vocal cord and the voice had greatly improved.

SUMMARY

The symptomatology and radiologic findings in a patient with neurofibromatosis and a neurofibroma of the right intrathoracic vagus nerve have been presented. The findings in this patient can probably be considered as characteristic of a neurofibroma of the intrathoracic vagus nerve.

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A STUDY OF INTERSTITIAL RADIATION OF THE DOG'S PANCREAS WITH RADIOACTIVE COLLOIDAL GOLD (Au^{198}) PRELIMINARY TO USE IN MALIGNANT DISEASES OF THE PANCREAS

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INTRODUCTION

THE current methods of treatment of carcinoma of the pancreas are not adequate and in many instances cannot be used because of the advanced stage of the disease. As shown by McDermott and Bartlett,[5] roughly 25 per cent are inoperable, 50 per cent are operable but not resectable, and only 25 per cent or less are resectable. Probably only 5 to 10 per cent of these are curable, at best. Therefore, the surgeon is frequently defeated before he starts, and his chances of effecting a cure are relatively small. Surgery, as suggested by Grönqvist,[2] is currently not the answer, whether it be for cure or for palliation by control of the tumor.

Other than surgery, we have only radiation for control of tumors in this region. Because of the deep anatomic location of the pancreas, external radiation has not proved practical. With the development of the radioactive isotopes, and the rapid increase in knowledge of and the skill in handling these isotopes, it was thought that an isotope might provide the answer, at least in part, to carcinoma of the pancreas. Because of its physical characteristics and rather widespread clinical use, radioactive gold (Au^{198}) in its colloidal form was selected for trial as a possible therapeutic agent.[12] After consideration of the special problems in relation to the pancreas and those problems inherent in the use of any radioactive isotope, an experimental project was prepared to study the applicability of using radioactive colloidal gold injected directly into the pancreas.

EXPERIMENTAL STUDY

In order to evaluate the effect of radioactive colloidal gold on the pancreas, an experimental problem was outlined using mongrel dogs as the experimental animal. It was hoped that this study would supply the answer to six questions or problems:

1. Can a suitable method of injection be developed?
2. What is the radiation hazard to the members of the operating team and to the personnel necessary for handling the dog in its postinjection radioactive state?
3. Since the radioactive gold is to be injected into an organ with a direct excretory system of its own, will there be any excretory loss either influencing item number 2 (above) or effecting establishment of a total dose?

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4. Would acute pancreatitis result from the direct injection of radioactive gold into the pancreas?

5. What would be the distribution of the radioactive gold not only in the pancreas itself, but also in neighboring lymph nodes, the liver, and other abdominal organs?

6. What would be the effect of the radioactive gold on the pancreas and other abdominal organs?

With these problems in mind, the following experiments were performed.

Mongrel dogs weighing 10 to 15 Kg. were used. All dogs were fed a standard kennel ration with no supplementary medication. No previous surgery had been performed on any dog and all dogs were examined at autopsy.

Method of Injection.—The radioactive colloidal gold was introduced into the pancreas under direct vision. With the dog under intravenous sodium pentobarbital anesthesia (10 mg. per kilogram of body weight), a standard midline, upper abdominal laparotomy incision was carried out. The tail of the pancreas was identified in the region of the hilum of the spleen, mobilized into the wound, and generally brought out above the surface of the skin. Extreme care was used not to injure the blood supply and to handle the pancreas delicately so that there would be a minimal amount of tissue reaction due to the surgery itself. A 4-0 silk purse-string suture was placed in the tail to hold in the solution after injection.

A standard No. 22-gauge spinal needle, 4 inches in length, was then inserted into the tail of the gland and down toward the body. The gland in this region is approximately 2 cm. in diameter and it was relatively easy to guide the needle through the center of the gland. The needle was inserted to a depth of 3 inches and then stabilized with gauze packing so that it moved only in relation to the gland and could cause little further trauma.

A standard 2 c.c. glass syringe was used, which was housed in a lead shield (Fig. 1). On the syringe was mounted a two-way (automatic no-return) stopcock. This was connected in such a fashion that the upstroke of the syringe piston would draw the radioactive material from its shielded container into the syringe. The downstroke would then deliver the contents of the syringe. The needle, stopcock, and gold container were all connected by means of 0.034 by 0.050 inch diameter polyethylene tubing and all connections were made with plastic tubing adapters. This proved to be a leak-proof system which functioned satisfactorily. The syringes were calibrated and found to deliver 0.65 c.c. per stroke.

The radioactive colloidal gold was used in the same container that it had been shipped in, and the only change was that at the time of use it was diluted with normal saline until its calculated activity was 5 millicuries per cubic centimeter.[1] Prior to connection with the prearranged needle in the pancreas, the system was completely charged with the radioactive colloidal gold. Three strokes of the syringe were employed, delivering approximately 1.95 c.c. of solution and approximately 10 mc. of radioactive material into the pancreas. These injections were made over a 2.5 cm. segment of the pancreas by withdrawing the needle slightly while the injection was made.

Following the injection, the needle was removed entirely from the pancreas. The sponges packing off the pancreas and maintaining stability were discarded. The puncture site was closed with the silk purse-string suture and the pancreas was returned to the abdominal cavity. The wound was then closed rapidly using routine surgical technique and the dog was returned to its cage.

The above method of injection and operative handling of the dog proved very successful. The actual operating time was very brief: the whole procedure required approximately 30 minutes. The equipment used was mechanically sound, cheap to obtain, and easy to assemble. It was readily sterilized and fairly durable. There were no operative deaths in the series.

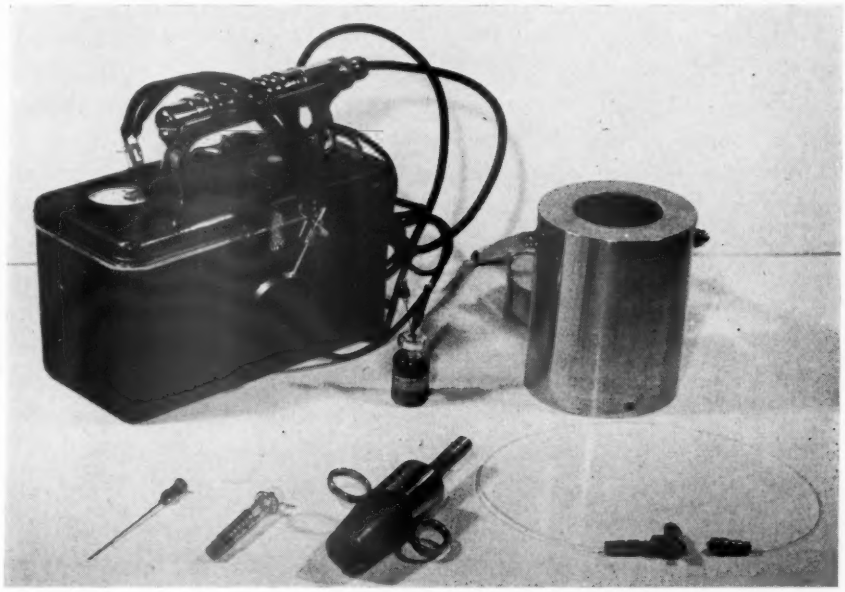

Fig. 1.—Equipment used in experiment. Bottom, left to right: Spinal needle, 2 c.c. syringe, lead shield for syringe, polyethylene tubing with stopcock and adaptors. Top, left to right: Portal count rate meter, Au^{198} in factory container, lead pot.

Radiation Hazard (Table I).—Since radiation does not involve any of the 5 senses, a sixth sense or some method of checking exposure was necessary. A standard portable count rate meter was used at all times (Fig. 1). It was constantly in use as a monitor during the operation, and at the end of the operation all surgical instruments, as well as the operative drapes and surgical sponges, were checked. In the instances when contaminated material was found this was

TABLE I. SUMMARY OF RADIATION HAZARD* INVOLVED IN PROCEDURE

1. Operating team	
A. Surgeon (6 dogs—60 MC.)	—13 mr.
B. Assistant (3 dogs)	
2. Equipment (contamination)	—minimal
3. Surface of cage	—10 mr. per hour
4. Urine and feces	—none
5. Laboratory personnel	—none

*Maximum safe weekly exposure—300 mr.

placed in a shielded container and permitted to decay prior to re-use. If the material was disposable, it was allowed to decay and then disposal was carried out.

All operating personnel wore individual ionization chamber counting devices in order to check exposure at time of operation.[9] In one operative and injection period, the operating surgeon handled 6 dogs, injecting a total of 60 mc. His exposure as shown by his personal ionization chamber was 13 milliroentgens, an average of 2 milliroentgens per dog. Since the maximum safe weekly exposure is established as 300 milliroentgens, these figures are well within tolerance.[9] Further, it is to be expected that six separate procedures would not be performed at one time when used clinically.

These low exposure figures were due to several factors.[8] The radioactive colloidal gold was never removed from its heavy container. The glass syringe had a lead shield of the same dimensions as the lead pot. The only exposed gold was the small amount in the polyethylene tubing and that coming from the dog itself. Since all beta particles were screened out either by the lead or by the animal's abdominal wall, only gamma radiation was received.[12] Exposure was further minimized by use of the inverse square law regarding distance and keeping actual time of exposure to a minimum.

Equipment contamination was minor. Of course, the polyethylene tubing and injecting needle were contaminated, but only on the inside, and these were discarded after decay or allowed to decay prior to re-use. The sponges packed around the pancreas were uniformly found to have one small area of contamination presumable from the tip of the needle on withdrawal. On two occasions, a hemostat was found to have been contaminated.

All other equipment, drapes and sponges were monitored and found to be safe. There was no contamination of the surgical gowns, while in several instances there was contamination of the surgeon's gloves. Two pairs were always worn since the lead syringe case was not sterilized. The outer pair were then discarded prior to closure of the abdomen.

Following return of the dogs to their cages, the surface of the cages was monitored. The maximum intensity was found to be 10 milliroentgens per hour during the first 24 hours and then there was progressive diminution with decay. This was well below excessive exposure level for cleaning of the cages and feeding and watering the animals. Even though these dogs were relatively isolated in one area of the kennel, the area exposure was always below that of 10 milliroentgens per hour.

All laboratory personnel who had any contact with the dogs, as well as the operating team, wore standard radiation film badges.[9] At no time was there evidence of exposure on either the beta portion or the gamma portion. It was assumed from this that total exposure to the radioactive animals and to the small amount of shielded radioactive material kept in the laboratory was well within the maximum safe weekly exposure of 300 milliroentgens.[9]

Excretory Loss.—Two dogs were placed in special metabolism cages. All urine and feces were collected for every 24-hour period, including washing down the walls of the cages. The portable count rate meter using its thin beta window

was used to scan the excreta, and at no time was there any evidence of radioactivity. Spot checks were run on the excreta of the remainder of the dogs at various intervals and at no time was there any evidence of contamination. There was, therefore, no loss in excreta.

Acute Pancreatitis.—The development of acute pancreatitis as a result of the injection of a possible irritating or stimulating material was checked in three ways: (1) serum amylase levels, (2) clinical observation, and (3) autopsy examination of the pancreas.

Three dogs were followed by means of preoperative amylase determinations as well as daily postoperative levels for a 3-day period (Fig. 2). In 2 dogs, the slight elevation was of no significance based both on the normal variation of the laboratory test and on previous experience showing a marked elevation in acute pancreatitis. In the other dog there was even a slight fall postoperatively. It was felt safe to assume that, by using the serum amylase level as a criteria, acute pancreatitis was not induced.

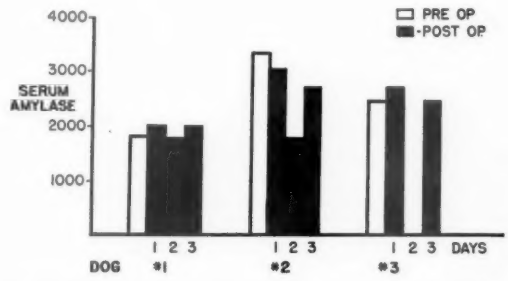

Fig. 2.—Serum amylase levels pre- and postoperative in 3 dogs.

Seventeen dogs were followed from a clinical standpoint in an attempt to identify acute pancreatitis. All dogs were up and about in their cages the day following surgery. They drank water and ate their normal kennel rations. Since previous experience had shown that dogs with acute pancreatitis were sick as manifested by lying quietly in their cages and refusing to eat or drink, it was felt that there was no pancreatitis. Further, dogs with acute pancreatitis without supportive therapy have a high mortality, and since there was no mortality in any of these dogs it seemed reasonable to assume there was no pancreatitis.

Last, all dogs were sacrificed, as early as 4 days after surgery and as late as 42 days after surgery. Some evidence of pancreatitis, acute or chronic, should have manifested itself at autopsy. Except for the area of injection which will be discussed later, the remainder of the pancreas was found to be entirely normal in all instances, nor was there any evidence of peritoneal irritation or change suggestive of pancreatitis.

It seems reasonable to assume, therefore, on a basis of the above three criteria, that pancreatitis was not induced in any of the 17 dogs, either from the surgical manipulation of the pancreas or the injection of the radioactive gold directly into the pancreas.

Distribution.—The distribution of the radioactive gold was studied in several ways: (1) gross observation of the tissue, (2) microscopic examination, (3) level of radioactivity in various tissues, and (4) radioautographs.

Dogs were sacrificed at 4, 11, 21, and 42 days, respectively, following injections. The fourth day was selected because the peak of the radiation effect would be reached at that time. The eleventh day was selected because by that time, approximately 97 per cent of the total radiation would have been delivered, but enough activity would remain for counting. The twenty-first day was selected because the early reaction would have subsided and distribution should have ceased. The forty-second day was selected because some of the late effects of radiation might be visible by this time.

Three dogs were sacrificed at 4 days following injection, and 3 dogs at 11 days following injection. Gross and microscopic examination showed gold particles in the site of injection and in the peripancreatic lymphatics in both groups. In the 11-day group, gold particles were found in the regional lymph nodes and some small amount in the liver. No gold particles could be seen in the remainder of the pancreas, the spleen, the duodenum, the stomach, the left kidney, or the left adrenal gland.

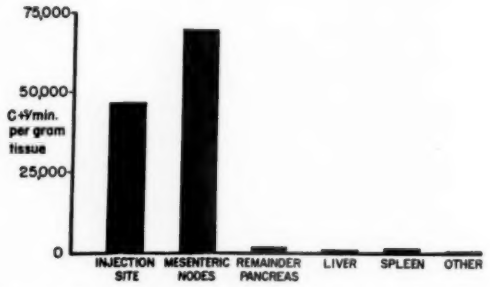

Fig. 3.—Tissue activity in Dog M2 showing distribution. 10 mc. in 2 c.c. solution, 11 days postinjection.

At the time of autopsy, specimens were taken from each organ as well as the various portions of the pancreas. These tissues were weighed carefully and then digested. Following digestion, the ash was resuspended in a measured volume of water and activity was measured by means of standard counting circuitry. From this the activity per gram of tissue could be determined, and by means of decay curves all tissues were corrected for decay to unit time. A final figure of corrected counts per minute per gram of tissue was obtained (Table II).

TABLE II. SUMMARY OF TISSUE COUNTING ON 6 DOGS

		TISSUE ACTIVITY COUNTS PER MINUTE PER GRAM TISSUE WITH CORRECTION FOR DECAY									
		PANCREAS									
SACRIFICED	DOG NO.	TAIL	INJECTION SITE	BODY	UCINATE PROCESS	MESENTERY	LIVER	DUODENUM	SPLEEN	KIDNEY	ADRENAL
4 days postinjection	10L	100	2,000	0	0	4,000	900	0	300	0	400
	7L2	600	40,000	0	0	100	900	0	100	600	200
	10U	800	—	0	100	75,000	300	0	100	0	100
11 days postinjection	5U	600	—	100	0	200	700	0	300	0	0
	M2	400	42,000	0	0	72,000	200	0	400	0	0
	5L	0	6,000	200	200	200	400	0	100	0	100

Because of the slight variation in total counts injected from dog to dog as well as the impossibility of assaying equivalent areas of tissue (especially in reference to site of injection), no comparisons of total activity could be made.

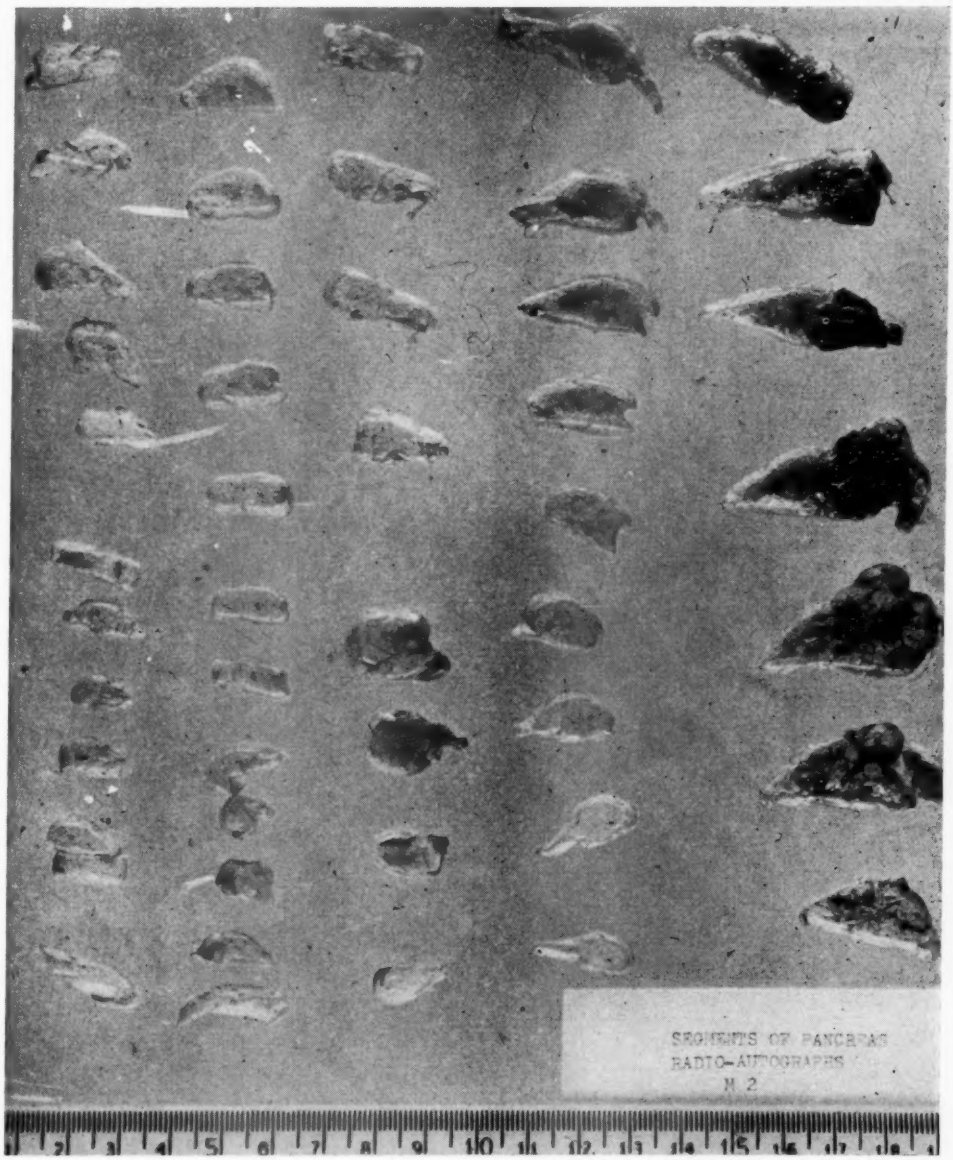

Fig. 4.—Sections of pancreas, 5 mm. thick, using every third section laid out on Pliofilm prior to making radioautograph. Notice localization of gold at the site of injection with local swelling.

However, it was possible in all instances to compare the amount at site of injection and in the neighboring mesentery and lymph nodes (the highest level of activity) with the activity of the more distant portions of pancreas as well as the other organs (Table II, Fig. 3).

It was found that a tremendous concentration of activity was present at the site of injection, in the neighboring mesentery, and in the neighboring nodes.

There was very little activity in the remainder of the pancreas and the rest of the organs. This bore out the gross and microscopic findings as to distribution of the gold.

A further study of distribution within the pancreas was made (Figs. 4 and 5). The entire pancreas was quick-frozen and then sliced into pieces approximately 5 mm. in thickness. Every third slice was used, and each piece in proper

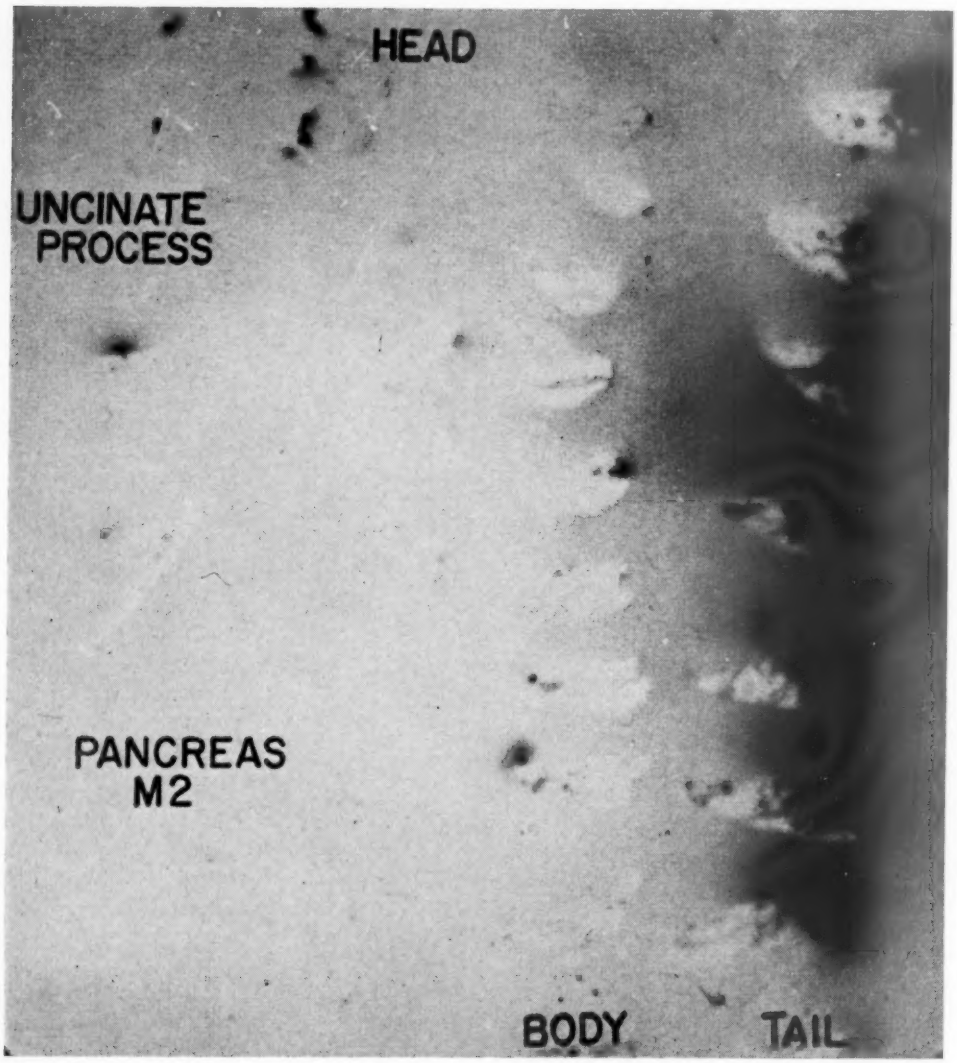

Fig. 5.—Radioautograph made from specimen shown in Fig. 4. Note activity at injection site and also lymphatic pickup.

alignment and order was laid out on a thin sheet of Pliofilm. Then the sheet of Pliofilm was placed over unexposed standard x-ray film and the slices were allowed to make a radioautograph. The entire time of exposure was carried out in a Deepfreeze to maintain the actual structure of the pancreas as much as possible. Time of exposure varied from 3 to 12 hours. These autographs show

tremendous concentration of activity at the site of injection (Fig. 5). There was no activity present in the remainder of the gland, except along several of the peripancreatic lymphatics.

These methods of study served to show that a high percentage of the radioactive material injected remained at the site of injection and did not distribute to the liver or other abdominal viscera.

Effect on Pancreas and Other Tissue.—All tissues were examined grossly and microscopically. In the dogs sacrificed at 4 days, the site of injection was markedly swollen, with areas of hemorrhage (Fig. 4). The retroperitoneal tissues and adjacent mesentery were also edematous. There were no other gross changes. When the injection site was cut into, black deposits of gold could be seen. On microscopic examination there were edema, hemorrhage, gold deposits, and large areas of tissue necrosis. This was confined almost entirely to the pancreatic injection site and the neighboring mesentery. No microscopic changes were found in the remainder of the pancreas, liver, spleen, kidney, adrenal gland, duodenum, or stomach (the latter two specimens were taken from regions adjacent to the injection site).

The findings in the dogs sacrificed at 11 days were very similar to those in the 4-day dogs. The edema and hemorrhage were still present, although the swelling was not quite as marked. Microscopically, the findings were similar to those of the 4-day dogs. There seemed to be slightly increased reaction in the mesenteric and retroperitoneal lymph nodes. Again, there was no reaction in the remainder of the pancreas and other viscera.

In the dogs sacrificed at 21 days, the amount of swelling was greatly reduced, but the injection site was readily identified. The retroperitoneal edema was gone, but the local nodes were enlarged and firm. Microscopically, there was marked necrosis of the injection site with gold particles present both free and in macrophages. There was much hemosiderin present. The lymph nodes showed deposition of gold and there was a marked lymphoid reaction. Gold was present in the spleen and liver in minute quantities. Again, there was no evidence of any reaction in the rest of the pancreas and the other organs.

In the dogs examined 42 days after injection, the site of injection was not grossly visible. However, on cut section, the black gold deposits could be seen and the injection site was firmer to touch. The retroperitoneal nodes were still enlarged and firm. Microscopically the pancreas showed fibrosis with marked destruction of architecture. There were gold deposits as well as deposits of hemosiderin. The neighboring lymph nodes showed some fibrosis and areas of gold deposition. There was also gold present in the liver and spleen and even gold as far away as the periadrenal lymphatics. No changes, however, could be seen in the remainder of the pancreas, liver, spleen, kidney, adrenal gland, duodenum, or stomach.

DISCUSSION

Since many of the carcinomas of the pancreas are inoperable at time of surgery and since, admittedly, cure by surgical excision is very rare, the use of radiation is the only other tool which is available at present. In general,

external radiation in the form of x-rays or even gamma radiation from a device such as a cobalt bomb or radium source has not proved applicable. This is due to the high level of radiation required for destruction of tumor tissue, with the resultant destruction of normal tissues.

Radioactive colloidal gold, however, may be placed directly into the pancreas. In this fashion, the radioactive material can be placed exactly where it should be, and because of the nature of its beta radiation, only tissues within at most 0.5 cm. would be affected (Table III). Further, the half-life of the gold is such that it is extremely applicable to human use, not to mention its availability and its ease of handling.[12]

TABLE III. SUMMARY OF CHARACTERISTICS OF Au^{198}

1. Half-life	—2.7 days
2. Beta ray	—0.97 MEV (3.8 mm. tissue)*
3. Gamma ray	—0.41 MEV
4. High specific activity	
5. High purity	
6. Low per cent ionic Au	
7. High rate of diffusion	
8. Lymphatic pickup	

*1 mc. per gram of tissue = 65,000 beta-equivalent roentgens.

It should be apparent that the described method is quite inexpensive, simple to operate, and satisfactory in function. In order to transfer applicability to the human, a slightly more elaborate setup would probably be needed, but the basic method would remain unchanged.

Certainly the radiation hazard would not increase in transferring the procedure to the operating room. Usually only one patient would be handled at a time. The same monitoring by means of the portable count rate meter would suffice. Theoretically, if a spill should occur, the operating room would be lost to use for only a few days—until the short half-life had brought about sufficient decay. As with the experimental animal, the decay period would apply to drapes, sponges, instruments, gown, and gloves, should they become contaminated. Certainly, the care of the patient following injection need not deviate from the system already established for patients with colloidal gold in the pleural or peritoneal cavities, especially since the amount of gold injected would remain approximately the same.[11]

As has been shown experimentally, there would be no apparent excretory loss nor would the gold be expected to spread beyond the site of injection.

As has been shown in the study, the effect on the other tissues would be expected to be minimal or nil. Although we try to avoid acute pancreatitis in the human subject, we are still able to handle it when it occurs, provided the diagnosis is made and proper treatment is instituted. Here, however, at least in the dog, we were unable to produce pancreatitis despite the fact that the dogs were deliberately fed immediately postoperatively. Certainly, the use of daily serum amylases would provide a means of following pancreatic activity.

As to the actual effect on the pancreas, the study indicated there should be almost complete destruction at the site of injection. This is, of course, to be

expected. In the irradiation of various tumors, it is felt that 5,000 to perhaps 10,000 roentgens are necessary for a tumor-killing dose. It has been shown that radioactive colloidal gold injected into tissue at a concentration of one millicurie per gram of tissue will deliver 65,000 roentgens equivalent physical to that gram of tissue.[5, 6, 13] This is roughly ten times the tumor-killing dose. Further, the radiation effect, being almost entirely due to the beta component, will not effect normal healthy tissue over 0.5 cm. away. This is perhaps the greatest advantage of using the radioactive colloidal gold. Another advantage is that the presence of a strong gamma gives an easy method for the external localization of the injected material. Further, the lymphatic pickup and distribution is ideal for tumor therapy.

Of course, the injection geometry must be more carefully worked out than was done in this experiment. More tissue must be infiltrated and, perhaps, pancreatitis may result. Certainly, in the prostate and in other tumors, experience has shown what dosages of gold and what volumes work best.[3, 4] In the dog, 10 mc. was placed in an area of approximately 8 c.c., or roughly 8 Gm. of tissue. Probably the human dose would not need to be as high. It is mandatory, however, that the gold be placed every centimeter in all three dimensions since only thus can adequate and equal radiation be delivered.

Thus, it would seem that the radioactive colloidal gold may be useful in the human patient with carcinoma of the pancreas. It should be of value in the inoperable case and perhaps even in what we now consider the operable case. Nor is it necessary that the use of the gold be confined to carcinoma of the pancreas, but it should be applicable to a host of other retroperitoneal tumors and perhaps other inoperable tumors of the abdomen. As with other radioactive isotopes, only the faintest beginnings into their usefulness have been made.

SUMMARY

An experiment was established to evaluate the use of radioactive colloidal gold in the pancreas. On the basis of the data obtained and the assumptions derived therefrom, the following findings were noted.

1. A method of injection at time of exploratory laparotomy has been described, evaluated, and found to be satisfactory.

2. The radiation hazard involved in injecting the radioactive gold into the experimental animal and in the care of the animal following injection was found to be minimal and well within the maximum safe weekly allowance.

3. Despite injection of the radioactive gold into a gland with an excretory duct, there was no loss of radioactivity, either in the feces or in the urine. Thus, the total amount of activity remained in the animal enabling dosage to be calculated and, further, there was no increase in radiation hazard.

4. Acute pancreatitis was not caused either by surgery or the actual injection of the radioactive gold in any of the experimental animals as demonstrated by daily serum amylase levels, clinical evaluation, and autopsy examination.

5. The injected radioactive colloidal gold was found to remain at the site of injection and in the neighboring mesentery and retroperitoneal tissues and did not spread to the liver, spleen, or other adjacent organs.

6. The radioactive colloidal gold caused almost total destruction of the pancreas at the site of injection, but caused no demonstrable effect on the remainder of the pancreas or on any of the adjacent organs, especially the liver.

A final suggestion was made as to future investigation, particularly in regard to injection geometry and the application of the radioactive colloidal gold to the human patient.

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EXPERIMENTAL BASIS FOR A NEW OPERATION FOR CORONARY ARTERY DISEASE

A Left Atrial-Pulmonary Artery Shunt to Encourage the Development of Interarterial Intercoronary Anastomoses

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THE present communication proposes an arteriovenous shunt between the pulmonary artery and left atrium as a surgical operation designed to redistribute blood entering an impaired coronary circulation in cases of ischemic heart disease. This type of shunt is a potent stimulus to development of interarterial intercoronary anastomoses.

EXPERIMENTAL STUDIES

Fifty selected healthy mongrel dogs of both sexes, weighing 15 to 30 Kg., were used. All animals were anesthetized with 3 per cent sodium Nembutal (30 mg. per kilogram of body weight) and were placed on a positive pressure respirator utilizing compressed air. Left-sided thoracotomy was performed in each case through the fifth intercostal space. The pericardium was opened parallel to the phrenic nerve to display the main trunk of the pulmonary artery and the left atrium. Sutures of 5-0 silk were used in side-to-side arteriovenous anastomoses varying in length from 10 to 24 mm. between the main pulmonary artery distal to the semilunar valves and the left auricular appendage. Preparation of the auricle required division of trabecular bands fortifying the thin wall. Creation of a right-to-left anatomic shunt permitted a fraction of returning mixed venous blood to bypass the lungs. After all operations, the thoracic cavity was closed in layers and 500,000 units of penicillin was given intramuscularly for 2 days. The pattern and distribution of the coronary arteries was studied at autopsy sacrifice 2 days to 4 months following surgery by injection corrosion preparations.[1] Studies of the architecture of the coronary arteries in normal dog hearts using the same injection method served as a control experiment. Circulatory adjustments in response to the shunt were investigated. Information included observations on blood hematocrit, hemoglobin, pH, oxygen content, and arteriovenous oxygen difference across the heart.

Calculation of the blood flow through the shunt was investigated in 5 preparations. Anesthetized dogs in a steady state were used. Oxygen consumption by the lungs per unit of time was determined employing the Benedict-Roth respirometer. Difference in oxygen concentrations of pulmonary

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artery blood (mixed venous blood), pulmonary vein blood, and systemic artery blood were determined. The Fick principle was applied to estimate the cardiac output, blood flow through the lungs, and blood flow through the shunt.

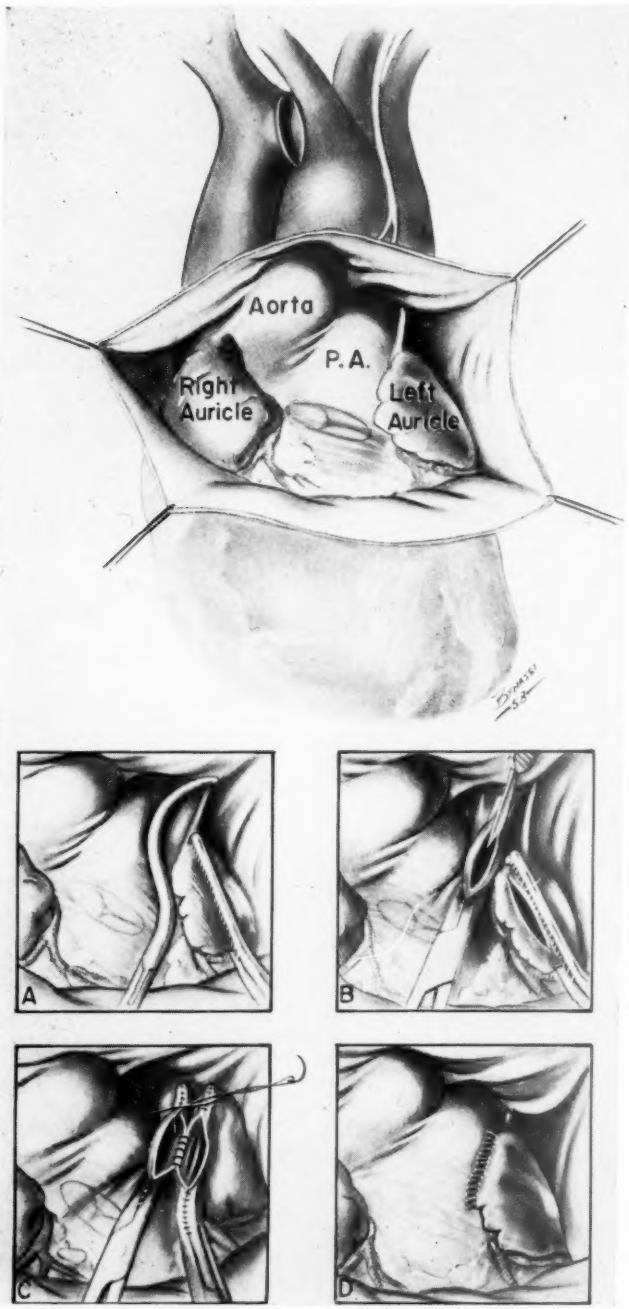

Fig. 1.—Anastomosis between pulmonary artery and left atrium within the pericardial sac. *A*, Vascular clamps placed on *side* of P.A. distal to semilunar valves, and across terminal appendage of auricle. *B*, Opening of vessels. *C*, Side-to-side approximation and suture anastomosis. *D*, Completed arteriovenous fistula with clamps removed.

Ten dogs were subjected to acute circumflex coronary artery ligation 2 to 4 weeks following surgery. The shunt was closed at reoperation prior to acute ligation.

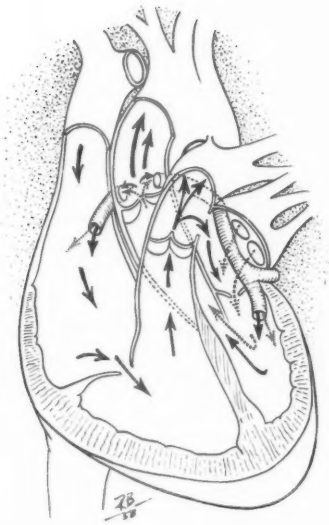

Fig. 2.

Fig. 3.

Fig. 2.—Circulation following shunt. Mixed venous blood (*black arrows*) enters right heart. In P.A. one fraction goes to lungs for oxygenation, one fraction bypasses lung through shunt. In L.A. this component mixes with saturated O_2 blood from pulmonary veins (*broken arrows*), two streams coalesce, pass via aorta into systemic circulation. Blood flowing through coronary circulation has, therefore, a reduced oxygen tension.

Fig. 3.—Di-cetyl phosphate band to close shunt. Scotch tape impregnated with di-cetyl phosphate is wrapped loosely around anastomosis. Gradual fibrosis of auricle in this region results in ultimate obliteration of shunt lumen.

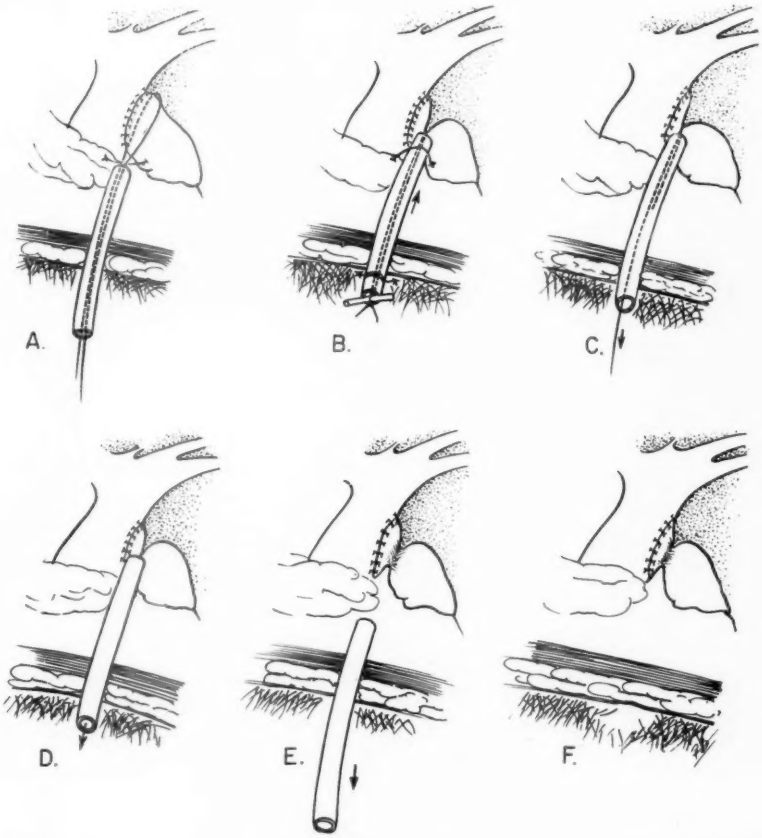

Fig. 4.—Polyvinyl snare to close shunt. *A*, Snare around anastomosis. Exteriorized through small bore P.E. tube. *B*, Traction on snare with counterpush on P.E. tube. Shunt lumen obliterated. *C*, Removal of snare by traction in direction of arrow. *D* and *E*, Removal of P.E. tube. *F*, Shunt closed with complete removal of prosthesis. Snare is left in place with lumen closed for 10 to 12 days before removal.

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OBSERVATIONS

The experimental production of interarterial intercoronary anastomoses and the circulatory adjustments to the hypoxemia provoked by this procedure have been reported in part.[2, 3] No operative mortality occurred. Postoperatively dogs with a fistula 10 to 12 mm. in length rapidly adjusted to the lowered tension of oxygen in the circulating blood. Thirty per cent of dogs with an anastomosis in excess of 20 mm. in length died within one month of surgery. Average values for arterial saturation in dogs with an arteriovenous anastomosis 10 to 15 mm. in length appeared to be constantly found in the limits of 75 to 88 per cent oxygen saturation.

The circulatory adjustments to this type of hypoxemia were characterized by a slightly greater coefficient of oxygen utilization than occurred in normal control dogs. Coincident polycythemia was a constant finding as indicated by an increase in hemoglobin and hematocrit values. Blood pressure did not appear to be markedly effected, nor did pressure values in the left atrium differ significantly following production of the shunt.[2]

Calculations of blood flow through the shunt (10 to 12 mm.) in animals of approximate size and body weight appeared to be in the area of 20 per cent of the total cardiac output.

Observations relevant to the acute circumflex coronary artery ligation studies are summarized in Table I.

TABLE I. SURVIVAL FOLLOWING ACUTE TOTAL CIRCUMFLEX CORONARY ARTERY LIGATION IN CONTROL AND EXPERIMENTAL ANIMALS

PROCEDURE PRIOR TO ACUTE TOTAL LIGATION OF CIRCUMFLEX CORONARY ARTERY AT ITS ORIGIN	NUMBER OF DOGS	TIME CHOSEN AS STATISTICAL BASIS FOR MORTALITY LIGATION STUDY—1 HOUR			
		DEAD IN 1 HOUR	PER CENT	SURVIVED 1 HOUR	PER CENT
Normal control dogs	25	18 All dead within 20 minutes of acute ligation	72	7	28
Creation of A-V fistula between pulmonary artery-left atrium 2 to 4 weeks preceding acute ligation study; shunt closed prior to coronary artery ligation	10	1	10	9	90

DISCUSSION

Intercoronary Anastomoses.—In our reported studies[1, 3] in no single demonstration was an interarterial anastomosis demonstrated between any branch of the right and left coronary artery in 50 normal dog hearts. Following the surgical production of an arteriovenous communication, 60 per cent of animals demonstrated the existence of inosculations, arterial in size, between branches of the right and left coronary arteries in animals sacrificed within one month of operation. In all cases (100 per cent) richly abundant intercoronary channels were present between major and minor rami of the left coronary artery. Only 30 per cent of control studies demonstrated comparable collateral vessels between rami of the left coronary arteries. Table I presents the results of challenging these vessels by acute ligation of the circumflex coronary artery.

Injection-corrosion casts of the distribution of the coronary arteries in the operated dogs provided an objective explanation for their survival following acute ligation. In all demonstrations (including one animal that fibrillated within 3 minutes) increased intercoronary channels were evident. In most preparations the circumflex coronary artery or its branches distal to the point of acute ligation was filled by retrograde flow of the injection mass from the left anterior descending artery.

Postmortem examination of the hearts prior to injection of the coronary arteries revealed that in 3 animals organized thrombus had occluded the shunt. Sufficient intercoronary channels had apparently been provoked, however, to enable the hearts to withstand the acute ligation. In 4 of the test animals normal cardiac rhythm was interrupted by ectopic beats within 5 to 10 minutes of ligation. This change spontaneously regressed in all cases and strong regular rhythm was restored in a further 10 to 15 minutes.

Lowered Oxygen Tension in Circulating Blood.—With respect to the heart, previous investigators have indicated that hypoxia may have beneficial influences until the concentration of oxygen reaches 9 per cent; then a circulatory crisis occurs.[10, 11] Sands and DeGraff[10] accounted for an increase in the minute flow of the blood through the body during anoxia as being due to an increased heart rate and a reduced peripheral resistance. Wiggers[11] confirmed this work and demonstrated that during hypoxia the ventricles eject blood with a greater economy of effort. In other studies, Hilton and Eicholtz[5] indicated an improved flow of blood through the coronary vessels during anoxic anoxia permitting an increased blood flow through the heart without change of arterial pressure. Subsequent studies have corroborated these findings, indicating that the volume of coronary flow increases greatly when the oxygen tension is reduced. That hypoxia is capable of exerting a powerful vasodilator action was demonstrated by Jochim,[8] who reported that preparations such as sodium nitrite, amyl nitrite, histamine, and certain xanthine derivatives are poorer vasodilators of the coronary arteries than is oxygen deficiency.

Lowered Oxygen Tension in Man.—These several observations including the presently reported development of interarterial intercoronary anastomoses suggest that there may be a lesser incidence of coronary artery disease in populations native to very high altitudes such as are found in the Peruvian Andes. Hurtado[6, 7] found in such Peruvian natives an oxygen content from 16.5 to 17.5 volumes per cent with an oxygen capacity of 19.2 to 20 volumes per cent, corresponding to an average saturation of 86 per cent in arterial blood. Comparative studies of the coronary architecture and a search for intercoronary anastomoses in the hearts of such individuals compared to a similar study in lowlanders might provide interesting data. Further importance may lie in the observations of Guzman-Barron[4] and Hurtado[7] that hypercholesteremia does not occur in acclimatized inhabitants of the Andes. If such observations be correct and if the prediction of an increase in interarterial anastomoses at high altitudes be substantiated, such findings would be

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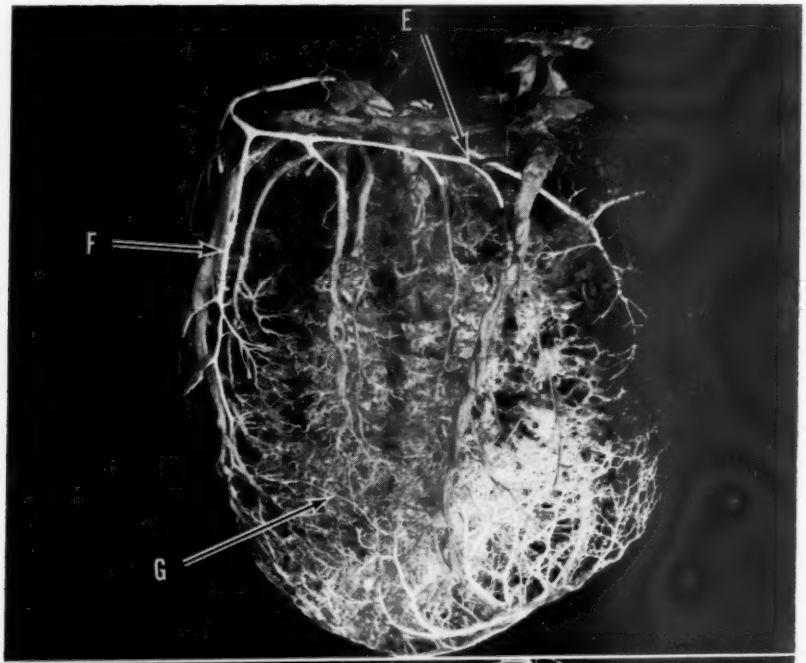
Fig. 5.



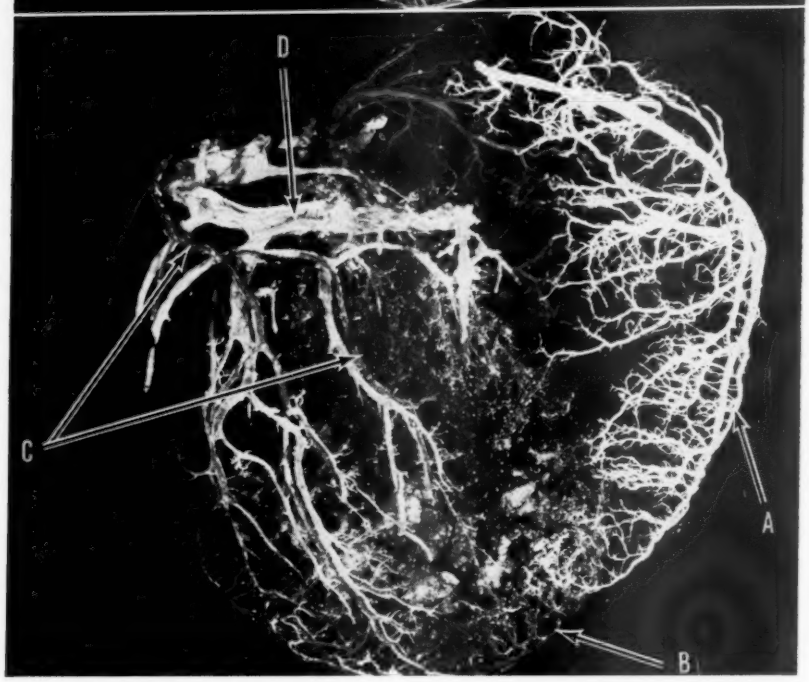


Fig. 6.

Fig. 5.—Vinyl plastic injection cast. Dog survived acute circumflex coronary artery ligation following shunt. Challenged 3 weeks after shunt. Note filling of circumflex coronary artery and branches distal to point of acute ligation by retrograde flow of injection mass. *E*, Intercornary anastomosis (large arterial in size) between circumflex branch of the left coronary artery and branch of the right coronary artery. *F*, Circumflex coronary artery branch. *G*, Intercoronary anastomosis between branch of the circumflex coronary artery and anterior descending artery.

Fig. 6.—Vinyl plastic injection cast. Dog survived acute circumflex coronary artery ligation following shunt. *D*. Coronary venous system. *C*, Branches of circumflex coronary artery filled by retrograde flow of injection mass from anterior descending artery (*B*). *A*, Right coronary artery and branches.

consistent with a lowered incidence of coronary artery disease. The existence of rich intercoronary networks in patients with congenital cyanotic heart disease (tetralogy of Fallot) has previously been related.[3]

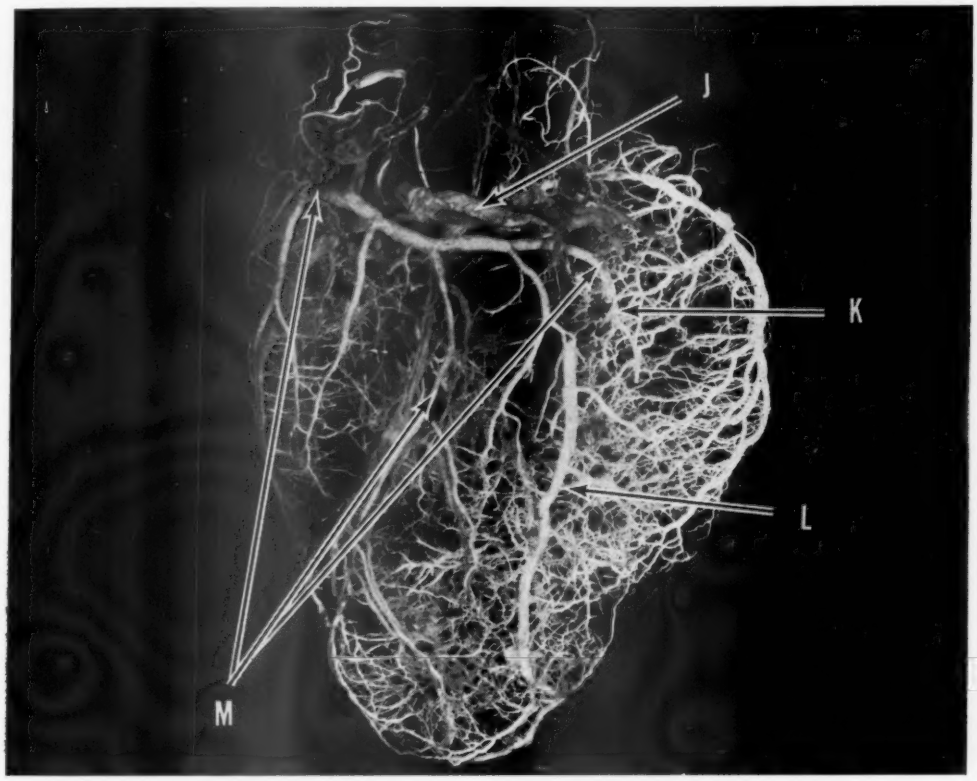


Fig. 7.—Vinyl plastic injection cast. Dog survived acute circumflex coronary artery ligation following shunt. Shunt created in this animal one week *after* acute ligation of posterior descending coronary artery at point (*K*), ligation of terminal end of left anterior descending artery, and ligation of terminal branch of right coronary artery. Following closure of shunt and acute total ligation of circumflex coronary artery at its origin one week later, animal recovered and was sacrificed 7 days later. Gross disposition of coronary arteries appears to be "normal." Circumflex coronary arteries and branches (*M*) injected by retrograde passage of plastic from anterior descending coronary artery. *J*, Coronary sinus. *L*, Posterior descending coronary artery.

The Present Study.—Intercoronary anastomoses have been provoked by a metabolic process and appear to be of such a size and speed in development that it is suggested that a method based on this approach might suitably be investigated in man with a view to its employment as a means of improving an impaired coronary artery inflow in patients suffering from myocardial ischemia. Zoll and his colleagues[12] have definitely demonstrated constant findings of anastomoses in hearts in which old, long-standing complete occlusions or extreme arteriosclerotic narrowing of the main coronary arteries had occurred. The present experimental observations indicate that a physiologic vasodilation of the coronary bed is provoked as a compensatory response to the circulatory changes induced by the hypoxia. In the light of observations reported by Krogh[9] and subsequently by other workers, it is likely that this vasodilation includes the capillary bed of the heart in addition to the arteriolar vessels.

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Thus, as a result of these and our other observations it appears likely that there is in response to this right-to-left shunt an immediate potent vasodilatation brought about by the desaturation and increased carbon dioxide content of the coronary blood, together with a continuing stimulus to anatomic proliferation of interarterial and intercoronary anastomoses.

The procedure is, therefore, presented as one for initial application to the large group of patients, selected by means of coronary arteriography, with severe degrees of obstructive coronary arteriosclerosis and not in cardiac decompensation from extensive muscle destruction. It is also suggested that the slowly obliterating atherosclerotic process in man will be a stimulus to insure that the channels provoked by the operation will remain open even if the shunt should close or be closed. By provoking these channels, prior to an occlusion in a major coronary vessel, the myocardium will be much better prepared to withstand a sudden thrombotic episode without muscle death or ventricular fibrillation as indicated in our experimental animals.

Exclusion of the shunt: We are of the opinion, based upon extensive experimental and clinical observations upon the physiologic effects of shunts, that an anastomosis of proper size in this location where pressure differentials are small may be left open indefinitely. However, in the event that this supposition is not universally applicable two methods to simply close the arteriovenous fistula have been investigated in the experimental animal.

1. At the time of operation a thin Scotch tape impregnated with di-cetyl phosphate has been wrapped loosely around the auricle at the site of anastomosis. Gradual fibrosis of the auricle in this region has resulted in complete obliteration of the shunt lumen within 10 days of surgery.

2. An alternative mode of closing the arteriovenous communication has utilized a simple polyvinyl snare, the loop of which is made to encircle the auricle near the site of anastomosis. The stem of the prosthesis is exteriorized through a small bore polyethylene tube. To close the shunt lumen, gentle traction on the snare with counterpush on the encompassing polyethylene tube is applied. The prosthesis is left closed in situ for 10 days. Both snare and outer tubing are then removed by withdrawing each segment of the apparatus under Pentothal anesthesia (Fig. 4).

In view of the remarkable tolerance of many animals to a small arteriovenous fistula and the rapid physiologic adjustments to the altered oxygen tension, the possibility of leaving the shunt permanently open in man is entertained.

SUMMARY

The observations recorded herein demonstrate that intercoronary interarterial anastomoses may be produced following surgical production of an arteriovenous fistula between the main pulmonary artery distal to the semilunar valves and the left atrium. Anastomotic communications arterial in size have been shown to develop within one month of operation. It has been shown that these vessels may afford protection to the heart of the dog when the coronary circulation is challenged by acute ligation of the circumflex coronary artery.

The physiologic trend of the circulatory adjustments to the hypoxemia induced by this procedure appears to be in a direction which would compensate for the lowered tension of oxygen in the circulating blood.

On the basis of these observations, it is suggested that this method of creating interarterial anastomoses should be investigated in man with a view to its employment as a means of improving an impaired coronary artery inflow in patients suffering from myocardial ischemia. Only clinical experience in man will define more precisely the advantages and limitations in such a method.

ADDENDUM

Since the preparation of this report the first patient has undergone a pulmonary artery-left atrial anastomosis for incapacitating coronary artery disease. This man, 47 years of age, was unable to work because of progressively more severe angina pectoris necessitating, in the months just prior to operation, the ingestion of an average of 100 nitroglycerine tablets per week. The patient's blood pressure and heart size were normal. His electrocardiogram was abnormal with typical ST and T-wave changes indicating myocardial ischemia.

Coronary arteriography was performed and disclosed widespread and extensive coronary arteriosclerosis. The main right coronary artery was completely occluded. The anterior descending branch of the left was completely occluded just distal to its origin. The left circumflex branch was patent and had only minimal atherosclerotic changes. This vessel constituted the main source of blood supply to the heart.

At operation on Dec. 26, 1958, the main pulmonary artery was joined to the left atrial appendage by a side-to-side anastomosis, 2.0 cm. in length.

The clinical response to this operative procedure has been dramatic and sustained to date. He has had no anginal pain and has not taken a single nitroglycerine tablet since surgery. He has returned to moderately heavy physical work. He is not visibly cyanotic, but his systemic arterial oxygen saturation has ranged from 84 to 88 per cent in serial determinations done postoperatively.

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Pediatric Surgery

CONDUCTED BY MARK M. RAVITCH, M.D.

INTUSSUSCEPTION

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WHILE intussusception is said to be the most common cause of intestinal obstruction in early childhood, the greater frequency of other sources of abdominal pain may prevent a prompt correct diagnosis. It is generally admitted that early and accurate recognition of this disease is the most important factor in successful treatment. Dependence upon typical signs of intestinal obstruction, a palpable mass, and blood in the stool may cause dangerous delay. To support these assumptions, we are submitting, supplemental to our report of 1956,[8] a review of 137 consecutive cases of intussusception admitted to the Denver Children's Hospital in the past 10 years and in comparison a like review of a smaller number admitted in the preceding 10 years. In the later period, the closed treatment has been utilized sufficiently to consider when it may be indicated and how it may influence early diagnosis and the end result.

The repeated emphasis on relation of early diagnosis to good results is again shown in our experience as our figures do not vary greatly from those of other representative reports.[3, 6, 10, 11, 14] In 185 cases admitted in 22 years preceding January, 1958, the importance of early recognition is plainly seen (Table I). The excellent results obtained in the first 24 hours seem independent of method of treatment. The increasing risk as time advances apparently loses its momentum after 72 hours due to a higher proportion of incomplete or recurrent nonstrangulating types.

TABLE I. DURATION BEFORE TREATMENT
(Jan. 1, 1936 to Jan. 1, 1958)

DURATION (HOURS)	NUMBER OF CASES	RECOVERED	DIED	MORTALITY (PER CENT)
0-24	99	98	1	1.01
25-48	33	29	4	12.12
49-72	23	19	4	17.39
Over 72	30	27	3	10.0
Total	185	173	12	6.48

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While it has been shown that the mortality of intussusception is dependent primarily upon duration before reduction, the better results of the last 10 years suggest that other factors are of great importance. These may include not only more accurate diagnosis, but also better recognition of fluid and electrolyte needs, the use of antibiotics, and perhaps methods of treatment (Tables II and III). Of the 40 cases in the earlier period, 4 died after definitive treatment and one died without it, giving a total mortality of 12.5 per cent and a treatment mortality of just over 10 per cent. By contrast, in the later period, in 137 cases, there was again a total of 5 deaths, only 2 of which followed definitive treatment. The over-all mortality was 3.6 per cent and the treatment mortality was under 1.5 per cent.

TABLE II. RESULTS OF TREATMENT
(Jan. 1, 1938 to Jan. 1, 1948)

Total number of cases admitted	40
Recoveries	35
Died following treatment	4
Died without definitive treatment	1
Mortality in treated cases	10.2%
Over-all mortality	12.5%

TABLE III. RESULTS OF TREATMENT
(Jan. 1, 1948 to Jan. 1, 1958)

Total number of cases admitted	137
Recoveries	132
Died following treatment	2
Died without definitive treatment	3
Mortality in treated cases	1.5%
Over-all mortality	3.6%

The literature records strong divergence of opinion as to choice of treatment, and convincing reasons have been given to support each preference. Proponents of prompt surgery[1, 3, 6, 12-14] state that (1) there is no time lost in the x-ray room and in waiting for results, (2) operative reduction is certain and positive, (3) any inciting cause such as polyp or diverticulum, if present, will be found and eliminated, (4) intussusceptions involving only small intestine can be plainly recognized and properly treated, and (5) perforation or gangrene can be seen clearly and handled correctly. Those favoring preliminary barium enema in selected cases[2, 7, 9-11, 15] emphasize the term preliminary and state that: (1) there is no tool of greater value for determining diagnosis and the need for surgery; (2) many unquestionable reductions are effected without surgery with consequent great economic gain and an expected lower hospital morbidity; (3) there is no actual time loss or delay as the half hour in the x-ray room is no more than that needed for operative preparations; (4) the presence of diverticulum or polyp as an obstructing agent is not overlooked if there is strict adherence in the selection of patients and if the criteria of successful reduction are fully satisfied; (5) every operation incurs some immediate and delayed risks for the patient including infection, the rare though possible cardiac arrest, and the later not so rare intestinal adhesions and obstructions; and (6) with the accepted pressures, perforation does not occur and gangrenous bowel does not reduce.[10]

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The relation of prognosis to the time element and the improving results in general have been widely emphasized. Comparison of methods of treatment as to outcome has been less often tabulated and may be worth recording here. The earlier period, 1938 to 1948, does not give much information in this regard except in contrast to the later period (Table IV). Not shown in the table are 14 appendectomies without mortality, 2 recurrences of intussusception after operation, 2 known later obstructions after operation, and 7 bowel resections with 2 deaths. The use of enema treatment was too limited to warrant any conclusions or any enthusiasm. The one death in an infant being prepared for operation after enema was not considered to have any relation to the short diagnostic procedure.

TABLE IV. METHODS OF TREATMENT
(Jan. 1, 1938 to Jan. 1, 1948)

Total number of cases admitted	40
Primary operation	32
Surgery after enema	4
Deaths after operation	3
Surgical mortality	8.3%
Primary enema	7
Successful reduction	2
Unreduced—operation followed	4
Unreduced—died before operation	1
Enema mortality	14.3%

Our experience in the second 10-year period is revealing. Of the 137 cases, 44 had primary operation and 46 had operation following enema (Table V). Two deaths followed operation, in each case preceded by enema. Both patients were desperately ill, both had high fever and abdominal distention, both were in the third day period, both showed pseudomembranous ileocolitis at autopsy, and one had an ulcer perforation. In the light of our present experience, neither one was ready for operation and indication even for diagnostic enema was doubtful. As in the earlier series, the surgical table does not show the 50 incidental appendectomies not accompanied by appreciable morbidity, the one recurrence, and the 3 known later intestinal obstructions. There were included 10 bowel resections; all of these patients recovered.

In this same period, barium enema was the primary treatment in 90 patients with positive reduction in 44 (Table VI). Reduction was considered unsuccessful or uncertain in 46, and operation followed, disclosing in 4 complete

TABLE V. OPERATIVE TREATMENT
(Jan. 1, 1948 to Jan. 1, 1958)

Total number of cases admitted		137
Cases treated operatively		90
Initial operation	44	
After enema	46	
Deaths without definitive treatment		3
Deaths following operation and enema		2
Total mortality		3.6%
Mortality after operation		2.2%

reduction of the intussusception. The mortality experience has already been described. Not shown in the table are 6 recurrences, with no later obstructions.

TABLE VI. PRIMARY CLOSED TREATMENT
(Jan. 1, 1948 to Jan. 1, 1958)

Total number of cases admitted		137
Primary barium enema		90
Successful reduction	48	
Surgery followed enema	46	
Found reduced	4	
Died after enema and surgery		2
Mortality in enema cases		2.2%

DISCUSSION

Regardless of the favorable aspects of closed methods and regardless of risk and longer hospital stay and the definite morbidity of any operation, it must be agreed that operation is a positive treatment for intussusception. That conclusion, however, hardly suffices condemnation of preliminary barium enema either as a diagnostic or as a therapeutic measure. To abandon preliminary hydrostatic trial in the rush to reach the operating room has been advocated, without statistical study or full consideration of the value of the procedure. The experience at this hospital in the past 10 years indicates that preliminary barium enema has a definite place in treatment as well as in diagnosis. The fact that almost one-third of the last 137 admissions were spared operation and sent home well in a matter of 48 hours is not to be summarily dismissed or blandly disregarded. In our series, no increase of hazard due to careful enema has been clearly demonstrated. As already mentioned, 2 patients died following enema and operation. Both were desperately ill patients in whom the result clearly was not affected by the short and nontraumatic enema trial. Actually more time was needed for surgical preparation to lower the temperature, to deflate the upper intestinal tract, and to establish fluid and electrolyte balance.

Enema reduction of intussusception (Table VII) had its highest success in the cases received within 24 hours of onset when 32 of 52 patients were spared operation. Even in the second 24-hour period, successful reduction was accomplished in 8 of 16 selected cases without subsequent operation. By contrast, in only one of 10 enema cases was reduction successful between 48 and 72 hours which would indicate, at least in this small series, that barium

TABLE VII. DURATION IN CLOSED TREATMENT
(Jan. 1, 1948 to Jan. 1, 1958)

DURATION (HOURS)	REDUCED WITHOUT OPERATION	OPERATION FOLLOWED	FOUND REDUCED AT OPERATION	DEATHS
0-24	32	20	3	0
25-48	8	8	1	0
49-72	1	9	0	2*
Over 72	3	9	0	0

*Both deaths followed operation.

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enema at this stage has little more than diagnostic value. That 3 of 12 cases had enema reduction after 72 hours points again to the special type of case often met at this late period. That 3 of the first 24-hour and one of the second 24-hour intussusceptions were found already reduced on operative exposure actually signifies little except to reiterate that operation is routinely recommended unless reduction is absolutely certain.

While primary closed treatment, especially in early cases, is steadily gaining favor at the Denver Children's Hospital due to its simplicity, its lower morbidity, and its economic saving, this method has definite limitations which must be stressed to avoid overenthusiasm. A succession of simple reductions may unduly encourage the unwary to conclude that this course is without pitfalls. As wider experience has been gained, enema reduction is not attempted, especially after the first 24-hour period, in the desperately ill or shocked patient or when clinical signs or a scout film show abdominal distention and obvious small intestinal obstruction. In cases where barium enema is to be given a trial, it is imperative (1) that the child be admitted to the hospital as an inpatient, (2) that a trained roentgenologist handle the actual technical procedure, (3) that the roentgenologist never be influenced to raise the barium column over 3 feet or to use any manipulation, (4) that there be absolute certainty of reduction as shown by complete outlining of the cecum and unrestricted filling of ileal loops, and (5) that the surgeon be close by to proceed with his plans for operation at the proper time and without delaying for clinical observation in doubtful reductions. The patient must remain in the hospital for 24 or preferably for 48 hours in order that recurrence or unreduced small intestinal obstruction may not be overlooked. A scout film of the abdomen before release may be considered an added safeguard. Only if all these rules are strictly observed should any attempt at closed reduction be permitted. Our results suggest more recurrences after closed reduction than after operation, while, on the other hand, later obstructive adhesions are limited to the patients who underwent operative procedures.

Since recognition of this disease within 24 hours of onset is of paramount importance, any course that will encourage admission to the hospital in the early hours must be commended. As has been well stated elsewhere, if mortality is to be further reduced[5] the surgeon's frontier lies in emphasis on earlier diagnosis rather than on method of treatment. At this hospital there is a steady trend toward earlier diagnosis with an increasing percentage of first 24-hour cases. One illustration of this trend is the early referral of patients who have some suspicious symptoms but not enough for clear diagnosis. It is gratifying that in the last 10-year period 34 patients with a tentative diagnosis of intussusception had scout films and barium enema showing no obstruction. Intussusception either was not present or already was reduced but the possibility was clearly in the mind of the medical attendant. It is certain, too, that other cases with colicky abdominal pain and reported blood in stools sent in for diagnosis but without the intussusception label were also being regarded with suspicion. One clinic reports with favor a far higher

proportion of cases with negative x-ray findings.[4] It has been mentioned elsewhere that a pediatrician is more prone to bring such a patient to the hospital if he expects a diagnostic barium enema rather than a diagnostic surgical exploration.

TREATMENT

A short description of the procedure followed in suspected cases of intussusception may be in order. When a patient is considered a good candidate for primary enema trial, he is sent immediately to the radiologist for a scout film and fluoroscopy. By no means are all patients considered good candidates. As shown in Table VI, about one-third of the 137 patients of the past 10 years did not have barium enema. Certain seriously ill patients, including those with shock, abdominal distention, or other advanced signs, are generally excluded, except that diagnostic scout films may seem indicated in some. In the selected cases, a nonlubricated No. 16 F. Foley catheter is inserted into the rectum and the bulb is inflated. A barium suspension is allowed to run into the tube under a gravity pressure of not over 3 feet. In a typical case, the barium may be seen to be arrested sharply at an obstruction. The flow may stop at this point or it may progress as the intussusception gives way. When the reduction is complete, the barium fills the cecum and many loops of ileum. If the reduction is not successful, the patient is allowed to expel the enema, then one or two more trials follow. Three trials are the maximum; no pressure greater than a 3-foot column is used, no anesthetic or manipulation is employed. Unless the cecum is completely filled along with many loops of ileum, reduction cannot be considered certain. An additional criterion of successful reduction is expulsion of the barium with flatus and feces associated usually with marked clinical improvement in the child, although the actual barium delineation is the true test. If, after this short trial, the radiologist has the least doubt as to complete reduction, operation is advised. It is recognized that there are cases in which the added relaxation of anesthesia may permit hydrostatic reduction impossible without it. However, statistical proof of the safety of this extension of the method is lacking. It is thought that tightness to the point of irreducibility without anesthesia should still be indication for open visualization and reduction.

As to procedure, following incomplete or doubtful reduction, the routine is well known. In all cases, with or without enema, dehydration, electrolyte imbalance, and blood loss should be corrected prior to surgery. A few hours at this stage may be essential to success. Our two failures in the last 10 years were accompanied by impatience with delay where more time might have changed the outcome. A right-sided incision is the usual one. Manipulation within the abdomen is gentle and the difficult final reduction may be helped by hot packs, prolonged gentle pressure, and possibly by glycerine between the layers. Routine appendectomy has been added by the majority of the surgeons unless there is some positive contraindication, and it has resulted in no apparent increase of morbidity. Bowel resection, if required, is done without hesitation and substitute measures have been rare. Adequate resection beyond the edematous area and immediate anastomosis have proved most satisfactory.

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CASE REPORTS

CASE 1.—C. C., a girl, aged 18 months, listless and grunting, had apparently had severe abdominal pain for 28 hours and had vomited repeatedly. A mass could be felt to the right of the navel. A scout film showed no abnormality of gas pattern. Under fluoroscopy, barium was seen to meet an intussusception in the transverse colon easily reducing it and filling a large amount of small intestine (Figs. 1 and 2). The patient went home the following day apparently well.

CASE 2.—D. C., a 4-year-old boy, with an indefinite illness of several days' duration had been vomiting during the past 24 hours and had passed one bloody stool. There was blood on rectal examination and a palpable mass in the right upper quadrant. On enema trial, barium was seen to meet an obstruction but advanced easily to the cecum. Since the cecum could not be filled out (Figs. 3 and 4) and ileal loops were not filled, operation was advised. An irreducible ileoileocolic intussusception was found and resected. The ileum was gangrenous. Duration was probably longer than 24 hours. There was no compromise when all reduction criteria were not met, and prompt operation was lifesaving.

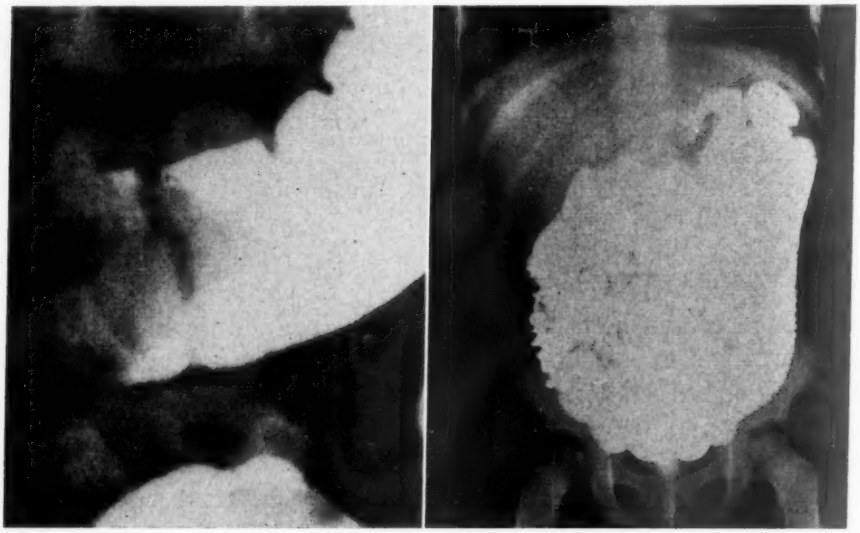

Fig. 1. Fig. 2.

Fig. 1.—Case 1. Intussusception met in the transverse colon.
Fig. 2.—Case 1. Intussusception reduced and the ileum filled with barium.

CASE 3.—T. R., a girl, aged 11 months, had been vomiting for over 3 days and seemed to have intermittent abdominal pain. There had been no stools. The abdomen showed moderate distention, no palpable mass, and no particular tenderness. Rectal examination gave no information. A scout film showed some general small bowel dilatation (Fig. 5), a warning not to persist in attempts at hydrostatic reduction. Barium introduced by rectum was arrested (Fig. 6) at the splenic flexure, and no further attempt at reduction was made. At operation, the invagination was found in the right colon and was easily reduced. This case is reported to emphasize that caution is the first consideration and that small intestinal dilatation is ordinarily considered an indication for operation.

CONCLUSIONS

A review of all the cases of intussusception admitted to the Denver Children's Hospital during the past 20 years is presented to consider in particular

Fig. 3.

Fig. 4.

Fig. 3.—Case 2. Intussusception reduced to the cecum but not into the ileum.
Fig. 4.—Case 2. Spot film shows persistent filling defect in cecum.

Fig. 5.

Fig. 6.

Fig. 5.—Case 3. Scout film shows general small bowel dilatation.
Fig. 6.—Case 3. Spot film shows barium arrested near splenic flexure.

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the relation of time, preparatory care, and method of treatment to results. The review is divided into two 10-year periods, the former having a treatment mortality of 10 per cent and the latter of 1.5 per cent.

Time is the most important factor in prognosis. Regardless of choice of treatment, nearly all cases treated within 24 hours recover, after which time there is a steady increase in mortality until 72 hours when the prognosis shows a slight improvement.

The value of operation as a positive approach to diagnosis and reduction is in no way questioned at this hospital. Barium enema clears the indication for operation and prevents many needless explorations. In the later 10-year period, the benefits of operation are attested to by the very low mortality, by successful bowel resection in 10 cases, and, incidentally, by added appendectomy in 50 per cent of the operations without apparent morbidity. Operation, however, according to our experience, is not a universal requirement in intussusception.

The use of barium enema is on the increase at this hospital. In the earlier 10-year period totaling 40 cases of intussusception, no conclusions can be drawn. In the later 10-year period, in 137 consecutive cases, 90 patients were selected for preliminary barium enema, of whom 44 or almost one-third of the total were spared operation which by necessity adds to hospital stay and morbidity.

Barium enema demands certain precautions which are cited in the discussion of technique and carries definite limitations. It is most valuable in the first 24 hours after onset, it still has a place in selected cases in the second 24 hours, but after that time successful reduction is rare. The procedure is usually contraindicated in the later hours, notably when shock, abdominal distention, obvious small intestinal obstruction, or high fever are present. For operation, too, delay for proper preparation is usually mandatory when these same conditions exist. With due consideration to these many factors, our results tend to agree that radiologically controlled hydrostatic pressure followed by operation if necessary to confirm or complete reduction is the treatment of choice in selected cases.

An increasing number of patients have been referred to the hospital with and without a tentative diagnosis of intussusception for diagnostic x-ray and necessary treatment. That a large number of these had negative findings points to the steadily increasing measure of suspicion that leads to earlier diagnosis and better results. Apparently the use of barium enema in these cases has encouraged the medical attendant to use the hospital at an earlier stage.

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CARDIAC SURGERY IN THE NEWBORN

Experience With 120 Patients Under One Year of Age

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THE highest mortality in congenital heart disease occurs in the first year of life. MacMahon, McKeown, and Record[22] estimate that among babies born alive with congenital malformations of the heart, 34 per cent are dead by the end of the first month and 61 per cent by the end of the first year. Richards and associates[29] have stated that 15 per cent die within the first month and an additional 12 per cent succumb by the end of the first year. Certain congenital cardiovascular anomalies are more lethal than others in the neonatal period and infancy. Gardiner and Keith[14] implicate tetralogy of Fallot and transposition of the great vessels as the principal malformations responsible for cardiac deaths in infancy. Other anomalies that are particularly serious during infancy include defects of the ventricular septum, tricuspid atresia, anomalies of the aortic valve and ascending aorta, and coarctation of the aorta. One might conclude that surgical correction should have widest application during early months of life in order to salvage critically ill infants.

Cardiac failure and anoxemia are chiefly responsible for the deaths occurring in infants with congenital malformations of the heart. Occasionally it is possible to effect striking improvement by careful medical management and, when feasible, this is the preferred treatment. A large number, however, are not greatly improved. Due to a significant morbidity and mortality associated with surgical treatment in this age group, in the past such infants were often denied the possible benefits of operation. The decision to postpone operation under these circumstances frequently leads to a tragic result. In some infants with intractable cardiac failure or anoxemia, operation on an emergency or semiemergency basis can be lifesaving. Surgical procedures performed in infants under these circumstances are destined to have a greater mortality associated with them than elective procedures performed at a later age. The important consideration is that in a significant number of infants death may be prevented by early surgical intervention.

During the past 4 years 120 infants under the age of one year have been surgically treated in the Texas Children's Hospital for congenital malformations of the heart or great vessels (Table I). All operations were performed

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on an emergency or semiemergency basis because of severe cardiac decompensation or anoxemia. Thirteen infants under one month of age were operated upon with 9 survivors. In 38 infants the operation necessitated use of a pump-oxygenator for temporary cardiopulmonary bypass. A direct attack has been possible in aortic stenosis, pulmonary stenosis, patent ductus arteriosus, ventricular septal defect, coarctation, and total anomalous pulmonary venous drainage. In the remaining lesions the surgical procedure consisted of establishing a shunt between the systemic and pulmonary circulations. The purpose of this paper is to relate our experience with these patients and to make certain observations and recommendations based upon these cases.

TABLE I. CARDIOVASCULAR ANOMALIES AND SURVIVAL IN 120 INFANTS LESS THAN ONE YEAR OF AGE TREATED SURGICALLY

LESION	NUMBER OF PATIENTS	AGE RANGE	LIVING
Ventricular septal defect	29	6 wk.—12 mo.	17 (59%)
Tetralogy of Fallot	28	3 wk.—11 mo.	22 (79%)
Transposition of great vessels	17	1 wk.— 7 mo.	10 (59%)
Coarctation of aorta	14	4 days—7 mo.	10 (71%)
Tricuspid atresia	10	2 days—8 mo.	7 (70%)
Patent ductus arteriosus	9	2 mo.—11 mo.	6 (67%)
Aortic stenosis	4	4 wk.— 6 mo.	4 (100%)
Pulmonary stenosis	4	2 mo.— 5 mo.	4 (100%)
Total anomalous pulmonary venous return	3	4 mo.— 6 mo.	2 (67%)
Single ventricle with pulmonary stenosis	2	4 mo.— 7 mo.	1 (50%)
Total	120		83 (69%)

VENTRICULAR SEPTAL DEFECT

During the past 2 years 165 patients of all ages with ventricular septal defects were operated upon utilizing a pump-oxygenator. Of this group 29 were infants varying from 6 weeks to 12 months of age. These infants were in severe cardiac failure frequently associated with infections of the respiratory tract. Response to medical therapy was considered to be unsatisfactory. An abbreviated cardiac catheterization was performed in most patients despite their precarious condition. In those instances in which it was measured, the pulmonary arterial pressure was significantly elevated.

The pump-oxygenator was used for temporary cardiopulmonary bypass in all patients. The large size of the defects frequently necessitated the use of a compressed polyvinyl or Dacron patch to effect closure without tension. Most of the defects were located in the membranous portion of the septum. In approximately half of the cases, associated anomalies existed including patent ductus arteriosus, atrial septal defect, coarctation of the aorta, and infundibular pulmonary stenosis. The youngest survivor was 3 months old at the time of operation.

Twelve infants (41 per cent) died following surgical correction of a ventricular septal defect in this group of 29 infants under the age of one year. The mortality rate is 7 per cent for the same procedure in patients between 2

and 15 years of age. Most deaths occurred within the immediate postoperative period in critically ill infants. A striking amount of medial hypertrophy of the pulmonary vessels was usually demonstrated at autopsy.

Defects of the ventricular septum are perhaps the most frequent cardiovascular malformations in childhood. Many infants apparently have difficulty in adjusting to increased pulmonary flow and pressure during the first year of life, and during this period death is most frequent. From a survey of 111 fatal cases of ventricular septal defect, Keith and associates[18] found that 38 had died under the age of one year. Complete correction of these defects has been possible only within the few years since the introduction and successful use of pump-oxygenators.

Despite a relatively high operative mortality, when the risks are balanced, it appears that operation is fully justified in infants if chances of surviving otherwise are poor. If cardiac decompensation responds to appropriate medical therapy, it is wiser to postpone surgical therapy until after the age of 2 years.

TETRALOGY OF FALLOT

Operation was performed in 28 infants under the age of one year with the provisional diagnosis of tetralogy of Fallot. The age at time of operation varied from 3 days to 11 months. The diagnosis was ordinarily established by clinical findings, although in a few instances abbreviated cardiac catheterization or angiocardiographic studies were performed.

In 14 infants a Blalock-Taussig[6] subclavian pulmonary artery anastomosis was created, and in the other 14 a Potts[28] aorticopulmonary artery anastomosis was used. Until 2 years ago, the criteria described by Blalock[4] were utilized to determine the type of anastomotic procedure. During the past 2 years with simplification of the Potts anastomosis, we routinely performed a left thoracotomy and utilized this procedure in all infants with a left descending aorta (Fig. 1). If the aorta descended on the right, a left subclavian pulmonary artery anastomosis was created.

Twenty-two infants survived a shunting procedure with improvement in 19 cases. Included in the successful cases was an infant 3 days of age at the time of operation. Two infants subsequently had a Blalock procedure performed on the opposite side because of recurrent symptoms of anoxemia. One of these died 4 days postoperatively and thrombosis of both anastomoses was demonstrated. The other patient has progressed satisfactorily. In the third child with an initially unsatisfactory result, successful complete anatomic repair was performed utilizing temporary cardiopulmonary bypass 2 years after the initial procedure.

Autopsy was performed in the 6 infants who died and all but one had lesions other than tetralogy of Fallot. Two cases exhibited a single ventricle, transposition of the great vessels, and pulmonary stenosis. In one case each, transposition with pulmonary atresia, single ventricle with pulmonary stenosis, and endocardial fibroelastosis was present. One infant in whom two Blalock procedures had been performed proved to have a typical tetralogy of Fallot

with thrombosis of both anastomoses at autopsy. It is thus apparent that the mortality occurred chiefly in those with complex lesions which were clinically confused with tetralogy of Fallot.

Extreme stenosis or atresia of the pulmonary artery frequently in association with severe dextroposition of the aorta is the usual cause of severe anoxemia in infants with tetralogy of Fallot. Syncopal episodes occur as a result of cerebral anoxemia and are the chief threat to life during the first year. In general, the decision to operate upon infants for tetralogy of Fallot was based upon the presence of frequent and severe cyanotic and syncopal episodes.

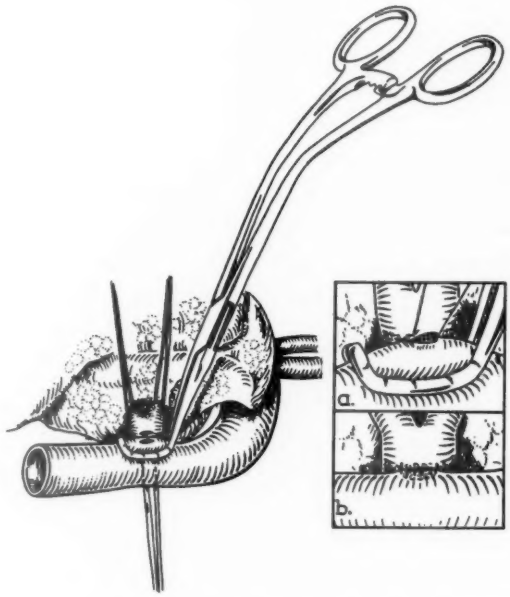

Fig. 1.—Illustration of anastomosis of aorta to the left pulmonary artery. Application of special partial occlusion clamp does not necessitate posterior dissection of aorta or division of intercostal arteries.

Although direct repair of the anomaly by open cardiac techniques would be desirable, in infants the mortality rate is excessive and difficulty would be encountered in creating an effective pulmonary outflow tract. Thus, in these severely anoxemic infants, one of the shunting procedures remains the operation of choice. This usually results in immediate and striking improvement and was accomplished with a 21 per cent mortality in the present series. This is not significantly greater than the mortality of 17 per cent reported by Taussig and Bauersfeld[30] for operative treatment of tetralogy of Fallot of all ages.

It is evident that an anastomosis performed in infancy may not increase in size with the growth of the infant and subsequent difficulty may ensue. This is substantiated by White and his associates[31] who found in a 5-year postoperative survey of the first 500 patients with a Blalock operation that the long-term results were most unsatisfactory in the infants under one year of

age at the time of operation. In the event that subsequent difficulty occurs, it is possible to interrupt the anastomosis and perform direct repair, as we have done recently, utilizing cardiopulmonary bypass.

TRANSPOSITION OF THE GREAT VESSELS

Seventeen infants, aged 2 days to 9 months, were operated upon for transposition of the great vessels. In 2 infants with associated pulmonary stenosis a Blalock operation was performed with death in one and improvement in the other. In 2 infants an attempt was made with the use of cardiopulmonary bypass to insert a prosthetic atrial septum in such a fashion that the caval blood was diverted into the mitral valve and pulmonary venous blood into the tricupsid valve. Both infants died. In 13 infants an atrial septal defect was created as described by Blalock and Hanlon[5] with improvement in 9 and death in 4. The youngest survivor was 12 days old. The peripheral arterial oxygen saturation in the survivors increased 11 to 32 per cent and moderate to striking clinical improvement occurred. We have not utilized the Baffes[2] procedure in this group of infants, preferring to reserve it for those patients over the age of 2 years.

Transposition of the great vessels is one of the most lethal congenital cardiovascular anomalies in infancy. According to Keith and his co-workers[17] approximately 85 per cent of those born with transposition of the great vessels are dead by the age of 6 months. Complete correction of transposition has not been accomplished, but significant benefit may be obtained from certain palliative procedures.

While many ingenious operative techniques have been devised for the correction of transposition of the great vessels, they have been associated with high mortality and partial success. In infants the most satisfactory results have been obtained from creation of an atrial septal defect. When anoxemia due to pulmonary stenosis is present, one of the systemic-pulmonary shunting procedures may be satisfactory. Although the operative mortality is high, it is not excessive when compared with the mortality in untreated cases and clinical improvement is often striking.

COARCTATION OF THE AORTA

Severe cardiac decompensation due to coarctation of the aorta necessitated operation in 14 infants under the age of one year. The ages of the infants at the time of operation varied from 4 days to 7 months. Diagnosis was usually easily established by determination of the blood pressure in arms and legs.

In 4 infants who were in the terminal stages of cardiac failure, the coarctation was of the infantile or preductal type and diffusely involved the aortic isthmus. Death occurred postoperatively in all 4 of these infants. In two of these the patent ductus was divided, the coarctate segment excised, and end-to-end aortic anastomosis accomplished. Death occurred within 24 hours in both infants. Autopsy examination in one of these infants disclosed a single ventricle with transposition of the great vessels and in the other mitral

atresia with both the aorta and pulmonary artery arising from the right ventricle. In the remaining two infants the coarctation was so extensive that it was considered impractical to attempt resection. Both infants died subsequently and were found at autopsy to have large ventricular septal defects.

In striking contrast to the 4 infants with preductal coarctation, all 10 infants with a postductal coarctation operated upon did well and had no further episodes of cardiac decompensation. A 10-day-old infant was the youngest to survive operation. A patent ductus arteriosus varying from 4 to 11 mm. in diameter was found at operation in association with the coarctation in all patients. When complete relief of cardiac failure did not occur postoperatively in one infant, cardiac catheterization demonstrated a ventricular septal defect. This was successfully corrected 6 weeks following resection of the coarctation. A ventricular septal defect is strongly suspected in another child but since this is asymptomatic, further diagnostic studies have been delayed.

The feasibility or resection of coarctation in the very young infant was reported several years ago by Kirklin and associates[20] and Baronofsky and Adams.[3] The lethal nature of coarctation during infancy was emphasized by Mustard and his co-workers[24] who found that 60 per cent of the babies with a postductal coarctation who present with symptoms in the first year of life die during that period. Of those with a preductal coarctation 89 per cent died in the first few weeks or months of life. Lang and Nadas[21] have recently reported the successful nonoperative management of 9 consecutive cases of coarctation with cardiac failure in infancy without a death but also noted that in a survey of the literature only 7 of 35 had survived nonoperative treatment.

In our opinion, any infant with severe cardiac failure due to a coarctation of the aorta should be explored surgically without undue delay. Since the adoption of this policy all infants with cardiac failure due to a postductal coarctation have survived. The 4 deaths have occurred in infants with preductal coarctation in association with other serious anomalies and it is doubtful that any form of therapy could have prevented death.

TRICUSPID ATRESIA

Ten infants with tricuspid atresia and diminished pulmonary blood flow were operated upon using a systemic-pulmonary artery shunting procedure. The ages of the patients varied from 2 days to 8 months. The youngest infant operated upon had a good result. Diagnosis was usually established on clinical, electrocardiographic, and radiologic findings.

The Blalock-Taussig anastomosis was used in 5 infants and the Potts anastomosis in 5. There were 3 postoperative deaths and in these congestive heart failure played a prominent role. The survivors were improved and the result was well maintained. In all survivors there was a moderate increase in the peripheral arterial oxygen saturation.

No attempt was made to create or enlarge an atrial septal defect. Although Neill[25] has reported a mortality rate of 18 per cent when an atrial

septal defect was created at the time of anastomosis as compared to 37 per cent when this was not done, we have not considered the procedure essential. The survival rate was 70 per cent in our patients under one year of age in comparison to a 30 per cent survival in the same age group reported by Neill. At this age a Potts anastomosis through a left thoracotomy is technically easier and the long-term benefit is not altered by creation of atrial septal defect.

In a survey of 111 cases of tricuspid atresia proved at autopsy, Keith and co-workers[18] found that 66 per cent died by the end of the first year of life. Death usually occurs from the effects of anoxemia. The prognosis appears to be particularly grave for those developing cyanosis within the first few days of life. In general, the prognosis for these patients is even worse than for those with tetralogy of Fallot and operation must be considered an emergency procedure in many instances.

PATENT DUCTUS ARTERIOSUS

Our experience has been limited to 9 infants under one year of age with patent ductus arteriosus in whom cardiac failure was of sufficient severity to justify closure of the ductus. In 5 patients the diagnosis was established on clinical findings. Aortography was performed in 3 and cardiac catheterization in one. In each patient the ductus was found to be large, approximating or exceeding the diameter of the aorta. Three patients died in the postoperative period. A 10-week-old infant died from atelectasis 48 hours later. Death occurred in another infant with multiple congenital anomalies. The third death was in a virtually moribund infant with a ventricular septal defect in addition to a patent ductus arteriosus.

Five of the survivors were greatly benefited while the sixth improved only moderately. This infant has a ventricular septal defect and a considerable degree of respiratory embarrassment results from bilateral bronchostenosis. The youngest infant surviving was 3 months old at the time of operation.

In certain infants with a patent ductus arteriosus cardiac failure occurs early, particularly if the ductus is of large caliber. Frequent respiratory infections, difficulty in feeding, and impairment of growth are characteristic. During infancy the murmur may be only systolic without the usual continuous quality typical of this lesion.[1] It is occasionally necessary to resort to retrograde aortography to establish the correct diagnosis. In infants with an additional left-to-right shunt at the atrial or ventricular level interruption of the ductus may result in sufficient improvement to allow delay of the definitive intracardiac procedure. Despite an operative mortality of 33 per cent, we believe that operation is indicated in any infant with severe cardiac failure due solely or partially to a patent ductus arteriosus.

CONGENITAL AORTIC STENOSIS

Among 21 patients with congenital aortic stenosis in whom valvulotomy was performed using the pump-oxygenator, 4 were under the age of one year. The ages of the infants at the time of operation were 4 weeks, 5 weeks, 2

months, and 6 months. All were in severe cardiac failure and one had experienced several episodes of syncope. The electrocardiograms in all demonstrated severe left ventricular hypertrophy and strain. Cardiac arrest from hemopericardium occurred in one infant 36 hours following direct left ventricular puncture for pressure measurements. The blood was evacuated from the pericardium by thoracotomy on the hospital ward. The infant was then transferred to the operating room and successful aortic valvulotomy accomplished during cardiopulmonary bypass.

In all of the infants operation was performed utilizing a pump-oxygenator. Induced cardiac arrest by injection of potassium citrate was used in one case but the practice was subsequently abandoned as unnecessary and not employed in the other patients. The stenosis was valvular in 2 infants, subvalvular in one, and combined valvular and subvalvular in one. The aortic valve was bicuspid in the 3 instances in which it was stenotic. The commissures were found to be fused and an adequate opening was obtained by cutting along the commissures. The commissural incisions were not carried completely to the annulus, in an attempt to prevent insufficiency. When stenosis occurred at the subvalvular level, the constricting diaphragm was incised and dilated.

All 4 infants subjected to operation for aortic stenosis survived. In one infant emergency thoracotomy was necessary 4 hours after operation because of hemopericardium produced by bleeding from the aortotomy. All infants improved clinically with electrocardiographic evidence of regression in left ventricular strain. In those in whom there was valvular stenosis a diastolic murmur is now audible but the clinical significance of this is undetermined.

The lethal nature of congenital aortic stenosis has been assessed by Braverman and Gibson[7] who found 6 deaths in a series of 73 patients with an adequate follow-up. One of the deaths occurred at the age of 3 weeks and one at 3 months. Marquis and Logan[23] discovered 5 deaths in 28 patients, one at the age of 6 weeks and one at 10 weeks. It is thus apparent that congenital aortic stenosis may have serious or fatal consequences during the first year of life.

In infants with cardiac failure due to congenital aortic stenosis, operation can be performed with acceptable risk and with good late results. The operation should probably be reserved, however, for those in cardiac failure or exhibiting rapidly progressive electrocardiographic changes. The degree and consequences of the postoperative aortic insufficiency remain to be evaluated.

CONGENITAL PULMONARY STENOSIS

In 4 infants, varying in age from 2 to 5 months, the manifestations of pulmonary stenosis were severe enough to demand emergency valvulotomy. There were no deaths. All of these infants had cardiac failure and dyspnea and the diagnosis was made on the basis of clinical, roentgenologic, and electrocardiographic findings.

The transventricular technique described by Brock[8] was utilized in all cases. A guillotine valvulotome was used to complete the incisions of the

valve. All of the infants had valvular stenosis, but one had infundibular stenosis in addition, and another had underdevelopment of the right ventricle. The right ventricular pressure at operation was quite high in those instances in which it was measured. The highest right ventricular systolic pressure recorded was 240 mm. Hg with a gradient of 220 mm. Hg in a 5-month-old infant. The right ventricular systolic pressure dropped to 45 mm. Hg immediately after valvulotomy.

Despite the existence of associated anomalies in 2 infants, all the patients were significantly improved by valvulotomy. In the child with an associated infundibular stenosis, recurrent difficulty 18 months after the initial operation necessitated infundibular resection. The child is now asymptomatic. The infant with underdevelopment of the right ventricle continues to have some difficulty and a peripheral arterial oxygen saturation of 70 per cent. The right ventricular systolic pressure, however, is 25 mm. Hg and there has been moderate clinical improvement.

Severe pulmonary stenosis with a normal aortic root and intact ventricular septum may have a fulminating course in infancy. In some instances the manifestations of pulmonary stenosis are so grave as to constitute a surgical emergency. Gibson and his associates[15] have emphasized this fact from a study of 45 patients with this valvular deformity. Ten deaths, 7 in children less than one year of age, occurred. The infants appear relatively normal initially, only to develop fulminant congestive failure or anoxia within the first few months of life. This usually necessitates prompt surgical therapy if death is to be prevented.

Although others have expressed dissatisfaction with pulmonary valvulotomy by the "closed" technique, we have been gratified by the results. In those patients in whom cardiac catheterization was performed before and after operation, a significant gradient across the pulmonary valve has not been demonstrated after valvulotomy. The results in these 4 infants emphasize the desirability of prompt valvulotomy in those with severe cardiac failure or anoxia resulting from pulmonary valvular stenosis. Tragic results may follow delay in surgery in severe cases during the first year. No evidence suggests that the benefit obtained from valvulotomy during infancy will not be permanent.

TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE

Three infants, aged 4 months, 4 months, and 6 months, respectively, with total anomalous pulmonary venous drainage were operated upon utilizing temporary cardiopulmonary bypass. In two of the infants total pulmonary venous drainage occurred into the left innominate vein through a vertical anomalous pulmonary vein, and, in the third, pulmonary venous drainage was into the coronary sinus. The technical aspects of the first successful complete correction of total anomalous pulmonary venous drainage into the left innominate vein were recently reported.[11] Correction was accomplished by use of a pump-oxygenator for temporary cardiopulmonary bypass. The atrial septal defect was initially enlarged, and an anastomosis was created between the posterior pulmonary venous chamber and the posterior aspect

of the left atrium. The atrial septum was repositioned to the right, thus closing the atrial septal defect and increasing the size of the left atrium. The vertical anomalous pulmonary vein was then ligated resulting in complete correction. Correction in those cases with complete pulmonary venous drainage into the coronary sinus was performed by enlargement of the coronary sinus ostium and repositioning of the atrial septum so that the coronary sinus emptied into the left atrium. The relatively small amount of unsaturated coronary return to the left atrium does not result in significant peripheral arterial unsaturation.

Two infants with total anomalous pulmonary venous drainage into the left innominate vein survived operation and had a completely satisfactory postoperative course. The infant with total pulmonary venous drainage into the coronary sinus was a lethargic 4-month-old infant who weighed 9 pounds, in whom death occurred 8 hours after operation.

Drainage of all the pulmonary venous blood into the right atrium via the systemic venous circulation may occur in several different forms.[12] Usually the pulmonary veins from both lungs converge to form a chamber posterior to the right atrium from which an anomalous vein emerges to join a systemic vein. In the most common form a vertical anomalous pulmonary vein, a remnant of the left superior vena caval system, connects the posterior chamber to the left innominate vein. In less common forms total pulmonary venous drainage may occur into the coronary sinus, directly into the right superior vena cava, directly into the right atrium, or into the inferior vena caval system. Survival depends upon a communication between the right and left sides of the heart, usually in the form of a patent foramen ovale.

Keith and associates[19] in a survey of 58 cases of complete anomalous pulmonary venous drainage report that 80 per cent died under the age of one year. Cardiac decompensation occurs early and is difficult to treat. While the diagnosis may be strongly suspected clinically, in infancy cardiac catheterization or angiocardiographic studies are necessary to confirm the presence of the anomaly.

Previous attempts at correction of total anomalous pulmonary venous drainage into the left innominate vein have usually consisted of anastomosis of the vertical anomalous pulmonary vein to the left atrium within the left mediastinum. Our experience, as well as that of others, with this procedure was unsatisfactory due to the necessity of displacing the heart during performance of the anastomosis and the small size of the anastomosis. The present operative procedure has made possible complete correction of the anomaly in infants without undue hazard. Due to the relatively high mortality in the untreated cases, surgical correction should be performed promptly.

SINGLE VENTRICLE

Two infants with a single ventricle, dextrocardia, and pulmonary stenosis were treated by performance of aorticopulmonary artery anastomoses. These cyanotic infants were aged 4 and 7 months, respectively, at the time of operation. Angiocardiography confirmed the diagnosis in both. Death occurred

from pulmonary edema 18 hours postoperatively in the 7-month-old infant. In the other infant the cyanosis has diminished and he appears moderately improved. The lesion known as single ventricle is usually associated with a rudimentary ventricle making direct repair almost impossible. Thus, the anastomotic procedures for single ventricle with associated pulmonary stenosis will remain the sole surgical procedures of value although results are strictly palliative.

COMMENT

In addition to the congenital cardiovascular anomalies which have been described, certain others may cause difficulty in infancy. Included in the latter group are vascular anomalies producing compression of the trachea or esophagus, ectopia cordis and diverticulum of the left ventricle, anomalous origin of the left coronary artery from the pulmonary artery, and atrioventricularis communis defects.

The most frequent vascular anomaly producing compression of the trachea or esophagus with significant symptoms in infancy is a double aortic arch.[16] Most humans with a double aortic arch have difficulty during the first few months of life and surgical therapy is frequently urgent. Due to extreme tracheal obstruction the infants with a double aortic arch have frequent superimposed pulmonary infections in addition to respiratory distress. Usually some interference with swallowing and active nursing is present. The roentgenologic findings in infants with double aortic arch have been elucidated by Neuhauser.[26]

In those infants with serious respiratory embarrassment, operative division of one of the arches can be performed with great benefit. Usually the anterior arch is the smaller and hence is the one which should be severed. Striking improvement in the respiratory status is noted immediately after operation.

The most frequent anomaly of origin of the coronary arteries is that in which the pulmonary artery gives rise to the left coronary artery. Infants with this anomaly appear normal at birth, but during the ensuing 2 to 3 months symptoms usually appear. Congestive heart failure may occur without preceding symptoms, but frequently episodes of pain and distress during and after feeding have been noted. The most striking roentgenologic finding is a greatly enlarged left ventricle. In most cases the electrocardiogram reveals a pattern similar to that associated with anterior myocardial infarction in adults.

Edwards[13] has recently re-emphasized the fact that, physiologically, a coronary artery arising from the pulmonary trunk creates an arteriovenous-like communication with blood flow through the anomalous coronary artery into the pulmonary artery. It is apparent that ligation of the anomalous coronary artery should result in significant improvement and this has been described by Case and his associates.[10]

In ectopia cordis the heart is displaced out of the thorax so that it lies on the anterior surface of the neck of the thorax or within the abdominal

cavity. The thoracic type, in which the heart protrudes out of the thoracic cage through a cleft sternum, is most common.[9] In the second most common type the heart extrudes through the diaphragm into the abdomen. Roentgenograms in the anteroposterior and lateral views confirm the abnormal position of the heart and may be of value in differentiating the condition from diverticulum of the left ventricle.

While a successful surgical correction of ectopia cordis has not been reported, it appears that the procedure might be feasible in the thoracic type. In the abdominal type the prognosis is considerably better—a few patients have reached adult life—and it appears that attempts to displace the heart from the abdomen would result in circulatory embarrassment.

Diverticulum of the left ventricle can be treated surgically with success. In this anomaly the diverticulum of the left ventricle, contained in a sac continuous with the pericardium, projects through the diaphragm and anterior abdominal wall to present in the epigastrium. The diverticulum is continuous with the left ventricular cavity. Symptoms usually occur in infancy and the majority do not survive the first few months of life. In the surgically treated cases the diverticulum was usually amputated while the base was clamped, followed by suturing of the myocardial edges.[27] Recent experience with postinfarctional aneurysms of the left ventricle suggests that excision during temporary cardiopulmonary bypass has many advantages.

The atrioventricularis communis defect includes any low atrial septal defect in which evidence of maldevelopment of the endocardial cushions is present. This may be manifested by abnormalities of the mitral or tricuspid valve with or without a ventricular septal defect. Symptoms frequently have their onset during infancy or early childhood due to valvular abnormality and an associated ventricular septal defect. The diagnosis usually depends upon cardiac catheterization and dye dilution studies. Eighteen patients over the age of two years with partial or complete atrioventricularis communis defects were operated upon utilizing temporary cardiopulmonary bypass with a mortality of almost 40 per cent. Many attempts at operative repair of these defects were in critically ill children with associated anomalies. A factor of great importance is the apparent vulnerability of the cardiac conduction system to injury during open repair of the defect. Due to the high operative mortality in children we preferred to treat infants with this defect nonoperatively.

SUMMARY

One hundred twenty infants under the age of one year have been operated upon for manifestations of congenital cardiovascular disease during a 4-year period. The decision to operate on all of these patients was based entirely upon the clinical impression that survival was not possible otherwise. Indeed, many of the patients were operated upon as an acute emergency particularly in the presence of severe cardiac failure or extreme cyanosis producing unconsciousness. Despite the critical condition of most infants, 83 (69 per cent) survived operation and were improved. In 13 infants less than one month of age, there were 9 survivors.

The lesions treated were ventricular septal defect, tetralogy of Fallot, transposition of the great vessels, coarctation of the aorta, tricuspid atresia, patent ductus arteriosus, aortic stenosis, pulmonic stenosis, total anomalous pulmonary venous return, and single ventricle with pulmonary stenosis. In 38 cases the operation necessitated the use of a pump-oxygenator for temporary cardiopulmonary bypass. Complete correction was possible for certain lesions while, in others, significant palliation resulted from increasing the pulmonary blood flow by the anastomotic procedures of Blalock and of Potts. On the basis of this experience it appears that early operation during infancy may be lifesaving in a high proportion of infants with serious cardiovascular malformations.

ADDENDUM

Since this paper was submitted 20 more patients less than one year of age have been operated upon with 3 deaths in complicated defects. Of particular interest is the fact that 7 patients with tetralogy of Fallot all survived operation, making an over-all survival in 35 patients of 82 per cent.

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Editorials

CONDUCTED BY I. S. RAVDIN, M.D.

The Period of Calm and Multiple Casualties

A sudden disaster in a city resulting in multiple injured persons should set in motion a series of prepared actions which will insure efficient care and a high rate of salvage. All of the basic facts underlying the handling of such an emergency are well known. Very briefly, first aid is carried out at or near the scene; the physician or physicians present then sort the patients and prepare for transportation; and finally various hospitals take over the definitive care. Smooth performance requires organized liaison with policemen, firemen, and trained lay persons; it depends upon prearranged plans with hospitals and prearranged plans for communication and transportation.

First aid implies assurance of an airway, control of external hemorrhage, bandaging, splinting, treatment for severe shock, evaluation of the extent of injury, and judicious control of pain. These measures are carried out near the scene of the accident. Equipment must be brought to the area; the patient is not taken to the equipment. Proper triage implies the presence of skilled doctors. Patients must be carefully checked, treated, and then prepared for the journey to forewarned hospitals. All of the casualties should not be sent to a single hospital, and certain types of injury, especially neurosurgical and thoracic, should probably be treated in certain hospitals designated for these specialties in the event of disaster. Burns, fractures, soft-part wounds, and abdominal injuries are best sent to several installations in order to distribute the load properly in the interest of better care.

It would seem that this is a reasonably simple plan. Far more complex problems are dealt with routinely during war and the answers are known. But a disaster in a city seems to be a signal for most persons to forget or disregard what they actually know. Numerous examples of this have been reported many times. Specifically, review the events after the crash of an aircraft shortly after take-off in Pittsburgh not so long ago. The radio stations immediately broadcast the news of the disaster. Typically this alerted the morbidly curious and resulted in a clogging of the main roads to the airport within an incredibly short period of time, preventing supplies to and patients from the area. As in other disasters, the pervading thought at the scene was "get the patients to a hospital right away." Since the roads were blocked to

the large hospitals in the city, almost all survivors were taken to a single smaller suburban hospital. Fortunately there were only eight, and they received good care. But what was so obviously wrong?

Leaving out of consideration entirely the harm that the immediate radio announcement did, it should have been recognized that there is a long "period of calm" from the time of the accident to the time when definitive complete hospital care becomes truly a necessity. This period is at least 4 to 6 hours for most injured persons, provided that first aid is practiced intelligently nearby and provided that adequate equipment and personnel can be made available there. This implies preplanning for the setting up of a temporary, sheltered holding station in the immediate area of any disaster, a "casualty clearing station." In the experience cited above such a plan would have allowed time for mobilizing proper transportation, clearing the roads, and preparing hospitals and surgeons in various hospitals for the work at hand.

What is needed is education and planning. Doctors should be organized throughout a large city so as to be available for directing the operation no matter where the accident occurs. Preplanning with police and fire departments, auxiliary ambulance services, and radio and television stations is a must. How will radio and television react to this implied request for early silence? Are the police ambulances properly equipped not only for individual injuries but for emergencies involving multiple casualties? Are persons trained in first aid organized and available for assistance? Do the doctors know that most Red Cross instructors carry essential equipment in their cars? They should all be part of the plan. And the plan should be actually tested by simulated alerts from time to time.

All of the hurry should be at the beginning only: to get personnel and supplies to the scene and to provide some sort of cover for proper first-aid care. Then the hurry is over and the "period of calm" begins, permitting efficient emergency treatment and sensible planning for definitive care.

How should such a plan be initiated? In small communities it emanates from the doctors in the hospital in the area. In cities more is needed than individual hospital organization, although this is, of course, essential. There must be a central top authority to coordinate the hospitals as well as all the doctors. This is best accomplished by the County Medical Society with the cooperation of Civil Defense and the American Red Cross, if these latter agencies are effectively organized.

—Samuel P. Harbison and David W. Clare
University of Pittsburgh School of Medicine

Report of the National Conference on Hospital-Acquired Staphylococcal Disease

In recognition of the seriousness and global scope of the problem of hospital-acquired staphylococcal disease, a National Conference was held in Atlanta, Georgia, on Sept. 15-17, 1958, at the Communicable Disease Center under the joint sponsorship of the United States Public Health Service and the National Academy of Sciences—National Research Council. The open sessions of this Conference were attended by 179 delegates who were consultants, members of the staff of the United States Public Health Service, research personnel, and representatives from 59 professional organizations and industrial concerns.

In the opening address, Dr. Leroy E. Burney, Surgeon General of the Public Health Service, outlined the purpose of the meeting to be a review of what is known about staphylococcal disease and what can be recommended as control measures and needed research.

Dr. R. Keith Cannan, Chairman of the Division of Medical Sciences of the National Research Council, indicated that the Council's interest in the problem stemmed from its study of the treatment of traumatic injuries, particularly burns, and the irrepressibility of the staphylococcus as an important cause of posttraumatic infection.

In summarizing the experience of the British, Dr. R. E. O. Williams of the Public Health Laboratory Service, London, indicated that there was no one way in which staphylococci spread within a hospital and no one prophylactic method by which their spread can be prevented. Since the routes of infection are numerous and often devious, the precautions needed appear to be many and complex. Preventive measures should minimize the endemic level of staphylococcal infections in an effort to prevent the emergence of epidemics and to terminate epidemics when they occur.

At the first general session, held on the morning of September 16 with Dr. I. S. Ravdin serving as Moderator, the staphylococcal disease problem was further delineated by a series of presentations pertaining to the emergence of hospital-acquired staphylococcal disease by Dr. Robert J. Anderson; the antibiotic resistance of the staphylococcus by Dr. J. Vernon Knight; and the staphylococcal disease problem in nurseries by Dr. Thomas E. Shaffer, on Surgical Services by Dr. Chester W. Howe, and on General Medical Services by Dr. David E. Rogers. The community aspects of hospital-acquired staphylococcal disease were discussed by Dr. Frederick H. Wentworth.

Following the first general session, 90 selected delegates, consultants, and authorities on staphylococcal disease were divided into three working conference groups of 30 each. The first, led by Dr. Warren E. Wheeler, considered the problem primarily in relation to the newborn nursery; the second, under the leadership of Dr. William A. Altemeier, considered the problem in relation to surgery; and the third, under Dr. Ivan L. Bennett, Jr., discussed the problem in relation to medicine.

These conference delegates agreed that drug-resistant infection has become a problem in practically all hospitals, not only in the United States but throughout the world. Serious epidemics have been infrequent so far but have occurred unexpectedly in many hospitals, usually starting in nurseries for newborn infants and in surgical wards. The disease has spread through the hospital and into the community at large by infected patients, many of whom may show little or no symptoms until after they leave the hospital. Although some hospitals have attempted to hide their problem for fear of causing public alarm or condemnation, some hospital administrators attending the Conference reported a growing awareness that open recognition of the problem is advisable as an aid in its control.

The staphylococcus is ubiquitous, and it was estimated that over 50 per cent of the population carry one or more strains on their skins or in their upper respiratory tract. This incidence is greater in hospital personnel because of the reservoir of drug-resistant strains permeating this environment. The problem of preventing serious infection then becomes one of determining which strains are dangerous, how they are spread, and how barriers can be devised against them.

The prevailing opinion of the Surgical Study Group was that that spread by personal contact was one of the most common, if not the most important, cause of staphylococcal hospital-acquired disease. The delegates recognized that the spread may also occur by contaminated air.

The major recommendations emanating from the three working discussion groups included the following:

1. Infection Control Committees should be organized in all hospitals and be given sufficient authority to investigate infections and to recommend hospital policies. The committee should include representatives from all major services, each of whom should have a keen interest in the problem. Meetings should be held at regular and frequent intervals. An important aspect of their work should be the training of hospital personnel in anti-infection procedures. Local health officials should be asked to serve as consultants to these committees.

2. An "Infection Log" should be devised for the recording and classifying of infections along with pertinent data. This would make it possible to determine if infections are increasing, if a local problem exists, and whether or not measures of control instituted are effective. The reporting of positive staphylococcal cultures by the laboratory to the Hospital Infection Committee would be an advisable step in keeping the "Infection Log."

3. All personnel having furuncles, carbuncles, or other active staphylococcal lesions should be excluded from contact with patients. This is an important aspect of prophylaxis. Unless a local problem exists, carriers harboring the staphylococcus in their upper respiratory tracts need not be excluded from the Operating Room area, provided they are adequately masked. Carriers with the same phage-type staphylococci as that concerned with the local problem should be excluded from contact with patients until they have been made free of this agent by treatment.

4. Patients with active staphylococcal disease should be isolated, particularly those with pulmonary and cutaneous infection. Because of the existing reservoir of virulent antibiotic-resistant staphylococci in hospitals, home care should be encouraged for patients with minor illnesses or other diseases which make them particularly vulnerable to staphylococcal infection. In addition to such factors as prolonged hospitalization and the usual hazards of surgical operations, other factors which appear to increase the susceptibility of surgical patients to hospital-asquired antibiotic-resistant infections include severe metabolic diseases, steroid hormone therapy, extension of operative treatment to poor-risk, aged, or debilitated patients, longer and more complicated operative procedures, prolonged treatment through indwelling plastic venous catheters, serious injuries, leukemia, or irradiation therapy. Such factors may lower the host reaction and increase susceptibility to infection.

It was strongly recommended that isolation techniques, which have fallen into disuse, be restudied and adopted for the segregation of active and virulent cases of hospital-acquired staphylococcal disease. Isolation should extend to certain patients who are especially susceptible to staphylococcal infection by virtue of other diseases or factors which decrease their resistance.

5. The indiscriminate use of antibiotics was discouraged, and their intelligent, thoughtful, and discriminate use was recommended. The routine use of antibiotics prophylactically in clean surgical cases was considered undesirable and dangerous.

6. Every effort should be made to overcome the physician's blind reliance on the use of antibiotic therapy and to discourage his false sense of security in their use.

7. The rebirth of surgical conscience, and everything that the term implies, should be fostered in view of the apparent importance of contact contamination. An intensive and continuous training program for medical students, interns, residents, staff physicians, and other professional and subprofessional personnel is important. To aid in these programs, the delegates recommended that the American Medical Association, the American Hospital Association, and the Public Health Service collaborate in the production and distribution of training films and other educational material. Such material should contain available information on environmental disinfection and the sterilization of equipment, linen, and other objects used in the treatment of patients.

8. The surgeon should make a sustained effort to establish and maintain the strictest plan of aseptic and antiseptic technique for all personnel in this area. Individuals not adequately trained in sterile technique should be eliminated from the Operating Room, as well as anyone having established staphylococcal disease. The sterile technique is fundamental in eliminating contact contamination, and methods of sterilization and antisepsis in use should be investigated by routine checks at regular intervals and re-evaluated. Personnel should not enter the Operating Room without removing street clothing and putting on operating suit, cap, mask, and shoes. It was pointed out that medical and other

consultative personnel have been particularly refractive in observing these necessary precautions. A re-evaluation of methods and preoperative preparation of the hands and operative area, draping, isolation techniques at the operating table, and of scheduling clean, contaminated, and dirty cases was recommended.

9. The growing evidence indicates that poor housekeeping techniques contribute to the development of the reservoir of antibiotic-resistant staphylococcal agents. Improved cleanliness, sanitation, adequate dust control, and more effective laundry procedures were emphasized for better housecleaning and housekeeping techniques.

10. No recommendations were made for changing existing hospital-ventilating systems until additional information has been obtained through research. The proper cleaning and maintenance of systems now in operation should be done routinely to facilitate the removal of dust, bacteria, and powder from the atmosphere.

11. A return to proved methods of careful and thoughtful dressing care was recommended. Dressing techniques have fallen into careless perfunctory procedures in which there is a need for gross revision. The adoption of adequate techniques would do much to eliminate contamination of the dressing cart's contents and to decrease cross-infection of wounds postoperatively. The difficulty in removing commercially prepared, presterilized, prepackaged gauze and other supplies, without contaminating them, was stressed. This trend of supplying gauze and instruments should be reviewed carefully and modified to insure sterility during removal.

12. Special precautions in nurseries for the newborn should be adopted, including the elimination of overcrowding and the maintenance of rigid sanitary and aseptic standards. Babies should be bathed immediately after birth with an antiseptic such as hexachlorophene. It was recognized that babies were the principal source of spread of the disease to the nursing mothers and into the community.

13. Competent bacteriologic laboratory services are essential to the diagnosis, treatment, and control of antibiotic-resistant infections. Laboratory services should be strengthened to provide adequate personnel and facilities for isolation, coagulase testing, and antibiotic sensitivity testing of the infecting bacteria. Bacteriophage typing in hospitals is recommended. However, since this is not practical for many institutions, it was recommended that the Public Health Service, through its own facilities and by assisting state and local health department laboratories, should aid in performing phage studies, particularly in epidemic situations.

14. Considerable confusion exists because of the lack of an adequate classification of postoperative wound infections. It is difficult and even impossible to compare data in published reports, past experiences, or different hospitals. It was recommended that a workable classification of staphylococcal disease be formulated.

15. An active research program is needed in the epidemiology of hospital-acquired staphylococcal disease and, in particular, to clarify the mechanism of

the development of bacterial resistance to antibiotics. Studies of desirable features in the design and construction of hospitals and hospital equipment are also needed. The delegates believed that not enough is known about environmental factors and the spread of infection to warrant recommending extensive or expensive changes in existing structures. This would include considerations to study the effect of environmental factors upon the spread of infection, to determine methods of measuring virulence of the staphylococci, and to review the basic immune mechanisms of the host to antibiotic-resistant infections in an effort to improve methods of host immunity.

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The Radical Surgical Treatment of the Perforated Gastric and Duodenal Ulcers

Thirty-six years have passed since J. Glatzel of Krakow advocated gastrectomy for perforated gastric and duodenal ulcer, performing this for the first time in 1918. There is still no unanimity on this very difficult and important problem. Many surgeons merely suture every perforated ulcer, even those in the stenogenic area. In my opinion this is wrong. Statistical data of the mortality rate are ±5.17 per cent for the partially gastrectomized group of perforated ulcers and 19.7 per cent for the sutured group. This is the average of the statistical data of seven great surgical centers.

The emergency gastrectomy is usually amazingly well tolerated, much better than simple suturing of the perforated ulcer. In my own group of emergency gastrectomies for perforated ulcer (42 patients), the average characteristics of recovery, mortality, febrile response, return of peristalsis, period of hospitalization, and so forth, were roughly the same as for a chosen group of 40 patients, subjects to a planned gastrectomy for chronic ulcer.

Skillful premedication and preparation of the patient, good anesthesia, and postoperative care are of outstanding importance. The late results are the most convincing argument for radical surgical management of the perforated ulcer. Sixty per cent bad results after suturing the perforated ulcer, including recurrent bleeding, secondary perforation, and a 20 per cent new growth development at the site of suture, are very convincing arguments for resection. This must be always kept in mind when managing a perforated ulcer. We also have to recall the fact that a secondary procedure is frequently difficult.

In my opinion gastrectomy of the Billroth I type for gastric perforated ulcer and of the Billroth II type (Rydygier method) for duodenal perforated ulcer are the procedures of choice. The Moynikan-Henle interloop type of gastrectomy may become the procedure of choice in the future, but as yet we have too little experience with it.

Sometimes in great statistics (±30 per cent) we may be forced by the general state of the patient to suture the perforation. We must remember that suture of the perforation is a palliative procedure. We ought to keep in mind all the benefits of radical surgical treatment of the perforated ulcer.

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In Memoriam

Daniel Collier Elkin

Daniel Collier Elkin, the only child of Robert L. and Roberta Collier Elkin, was born in Louisville, Kentucky, on March 26, 1893. His life was enriched by the heritage of his keenly intellectual, public-spirited parents, who were constantly aware of their responsibility and concern for the welfare of the community.

His childhood was spent in Lancaster, in central Kentucky, which was the home of his forebears who were early settlers in Garrod County. His mother was responsible for much of his gentle spirit and interest in the welfare of his friends and associates. His father was a newspaper publisher and farmer, with interest in breeding and judging fine horses.

Following a well-rounded and happy childhood, he proceeded to Phillips Andover Academy, preparatory to his entrance to Yale University. At Yale, he developed a keen interest in the traditions and achievements which have made that institution great. His loyalty never ceased and he availed himself of every opportunity to support his Alma Mater. In 1948, he served on the Committee for Medical Affairs.

He entered into all school activities at the University and his natural leadership capabilities were soon recognized. He was elected a member of Delta Kappa Epsilon, Scroll and Key (Senior Society), and the famous Whiffenpoofs. His athletic interests were not excelled by his scholastic achievements. One of his choicest prizes was that of membership on the Yale crew. On finishing Yale, Dr. Elkin entered Emory University School of Medicine and graduated with honors in 1920.

Dr. Elkin's attraction to medicine began early. He was influenced, no doubt, by his uncle, Dr. William Simpson Elkin, who was one of the real pioneers in modern medical education. Dr. William Elkin was instrumental in amalgamation of the medical schools in Atlanta and the establishment of the school which became the present Emory University School of Medicine, which he served for 25 years as Dean.

Daniel Elkin was appointed to the house staff of the New York Lying-In Hospital, New York City. In 1921 and 1922, showing an interest in teaching, he was made an Assistant in Anatomy and an Instructor in Obstetrics and Gynecology at Emory University. He then entered Peter Bent Brigham Hospital as an intern and remained until 1924. During his last year there he was Resident in Surgery under the illustrious Dr. Harvey W. Cushing whose influence meant much in Dr. Elkin's developing interest in research and teaching.

Following completion of the residency in surgery, he returned to Atlanta and practiced surgery with his uncle, who enjoyed quite an extensive private practice. He actively assumed teaching responsibilities in the Emory University School of Medicine, beginning as an Instructor in Surgery. In 1930, he was appointed Professor and Chairman of the Department of Surgery and Surgeon-in-Chief of Grady Memorial Hospital. He held these positions until 1939, when he was appointed Joseph B. Whitehead Professor of Surgery and Chairman of the Department. He continued as Surgeon-in-Chief of both Grady Memorial Hospital and Emory University Hospital.

This was the beginning of Dr. Elkin's fruitful years in surgery. His interests were broad, although he soon concentrated on thoracic and vascular surgical problems. This occurred in the formative period of these specialties, which was stimulated by the abundance of material in the local hospitals. His contributions to vascular surgery have been outstanding, particularly related to the early operative procedures on the heart, appreciation of the hemodynamics in cardiovascular disease, and specifically, in understanding of the physiology of arteriovenous fistula.

In 1942, Dr. Elkin was called to active duty in the Armed Forces and was assigned, by the Army, as Chief of Surgery at Ashford General Hospital. Due to his influence, this became one of the outstanding vascular centers in the nation. Moreover, through his efforts, these centers were established to furnish the most skilled assistance for correction of these disabilities. The report which was recently published by Drs. Elkin and De Bakey, "Vascular Injuries of World War II," stands as a monument to their interest in the development of the treatment of these injuries on a sound basis. On return from the Army, in 1946, Dr. Elkin again assumed Chairmanship of the Department of Surgery at Emory University School of Medicine and he remained until his retirement in 1954.

To account the many accomplishments of Dr. Elkin would require far more than this short tribute. He was early recognized as a leader and was accepted and admitted to membership in most of the professional surgical organizations. He contributed greatly toward their growth at a time when surgery was assuming its rightful role, in perhaps the most progressive period in the history of medicine. His wise counsel, ready wit, and unfailing interest in the development and well-being of surgery did much toward elevating it to the high plane which it now occupies. Interestingly enough, Dr. Elkin was made president of most of the major surgical organizations of which he was a member. He was long active in the American College of Surgeons and, in 1956, was made president of this organization. He was President of the American Surgical Association, the Southern Surgical Association, and many others.

Dr. Elkin was in frequent demand as a lecturer, and on many occasions served in this capacity for national organizations. He frequently was a guest lecturer for many medical schools and was also sought after as a commencement speaker.

His interest in national affairs was second only to his interest in surgery. He served on numerous advisory committees for medical affairs. He was a member of the National Research Council and was Chairman of the Council in 1951.

One of the crowning achievements of Dr. Elkin's career was the Chairmanship of the Centennial Committee of Emory University School of Medicine. This was a historical event in the accounting of important roles this school has occupied in medical educational affairs in the community. It is needless to say that Dr. Elkin entered into this celebration with the same enthusiasm with which he was so capable.

Dr. Elkin was a prolific writer and contributed much to medical literature. His subjects were varied and were noted for their clarity and scholarly presentation. His personal correspondence was voluminous and was characterized by broad interest and the ability to express ideas in a well-chosen manner.

To Dr. Elkin many honors were given. He was recipient of several honorary degrees and membership in numerous learned societies other than medical. One outstanding award was the Rudolph Matas medal, presented by Tulane University, in 1940, for his unusual contribution to vascular surgery.

Dr. Elkin's family life was of great importance in his achievements. In 1923, he was married to Miss Helen McCarty. He is survied by his wife, his son, Daniel C. Elkin, Jr., and grandson, Robert Elkin. His concern for his family was an example of unselfish devotion.

Dr. Elkin wore all of his many honors and successes with much modesty, dignity, and humility. Frequently, he credited to others the achievement for which he was in a great measure responsible.

At his retirement as Professor of Surgery of Emory University School of Medicine, Dr. Elkin returned to his native Lancaster, Kentucky. Although inactive in his former pursuits, he was not one to sit idly. His advice and counsel were constantly sought. He was appointed a member of the Board of Trustees of the University of Kentucky and the Kentucky Foundation and has been instrumental in the establishment of a medical school at that University. Not the least of these interests was his leadership in the restoration and support of the Ephraim McDowell Memorial in Danville, Kentucky. Only a few hours before death, he was discussing the means of raising funds for the permanent support of his memorial, which he cherished so much.

In the passing of Dr. Elkin, medicine has lost a true scholar, an inspiring teacher, a diligent investigator, but above all, a courageous leader. His life and teachings, however, will continue as an inspiration to his innumerable friends and to many students of the present and future.

—J. D. Martin, Jr.